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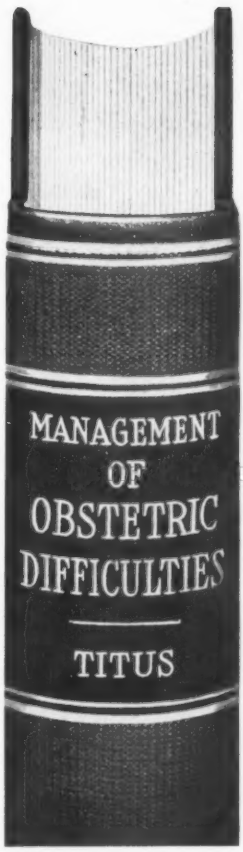

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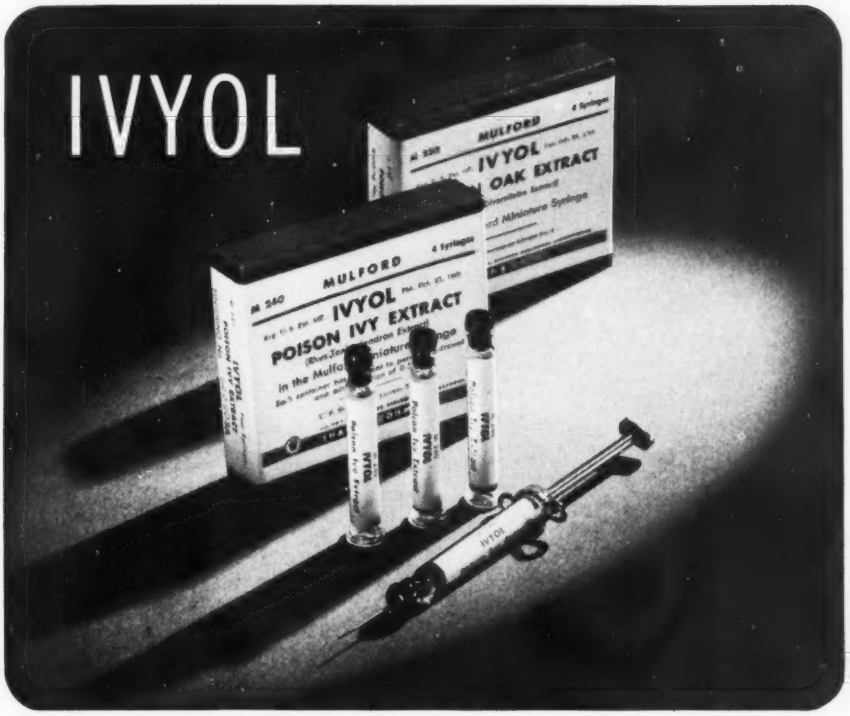

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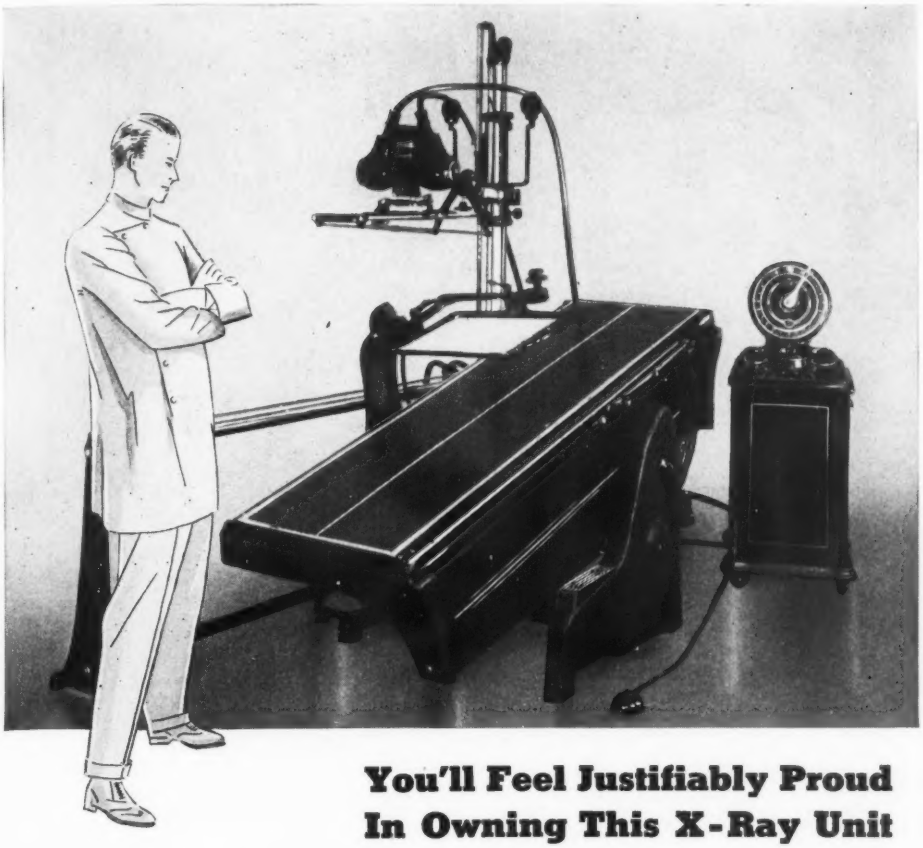

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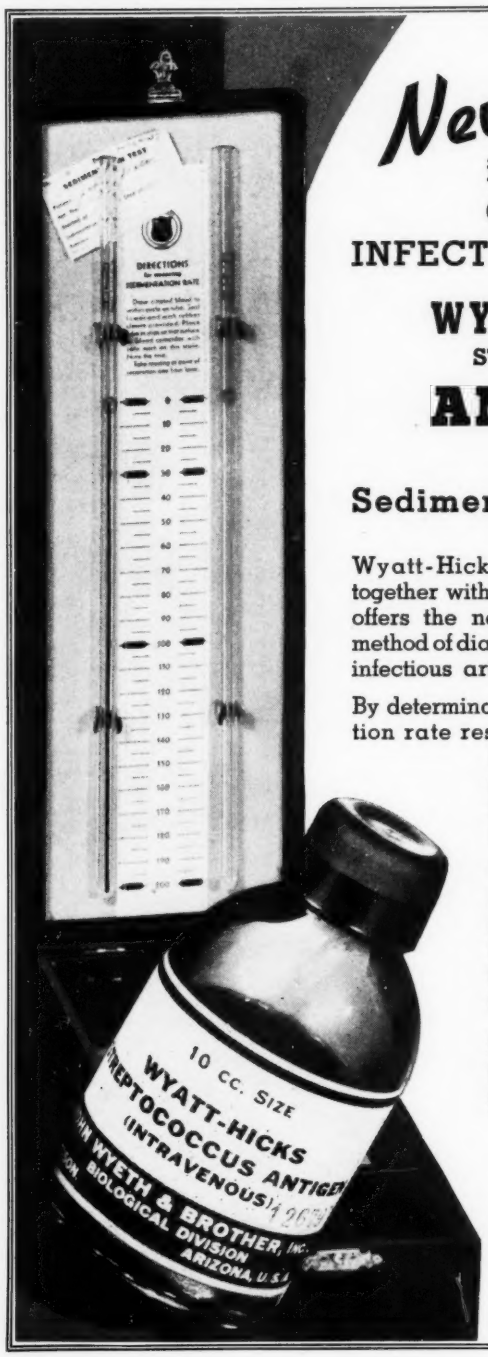

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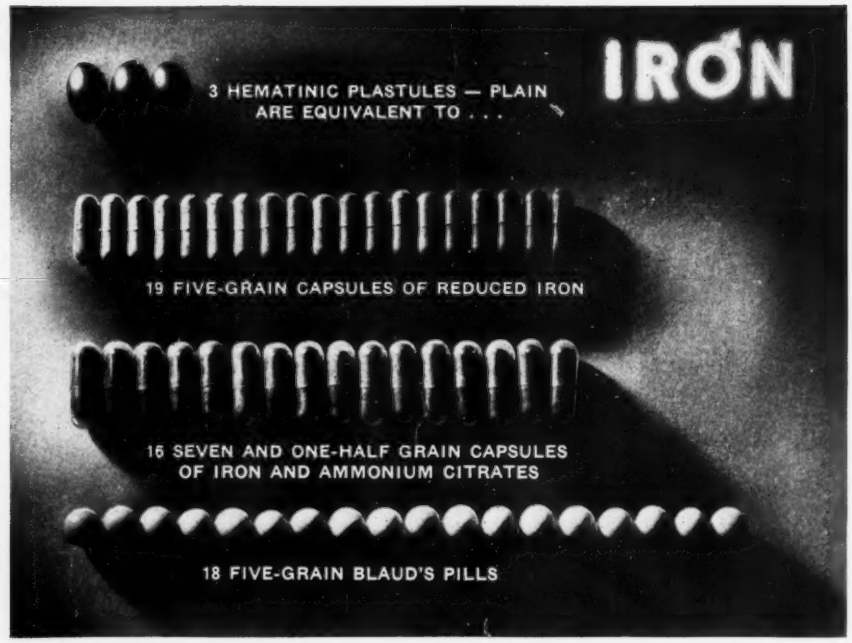
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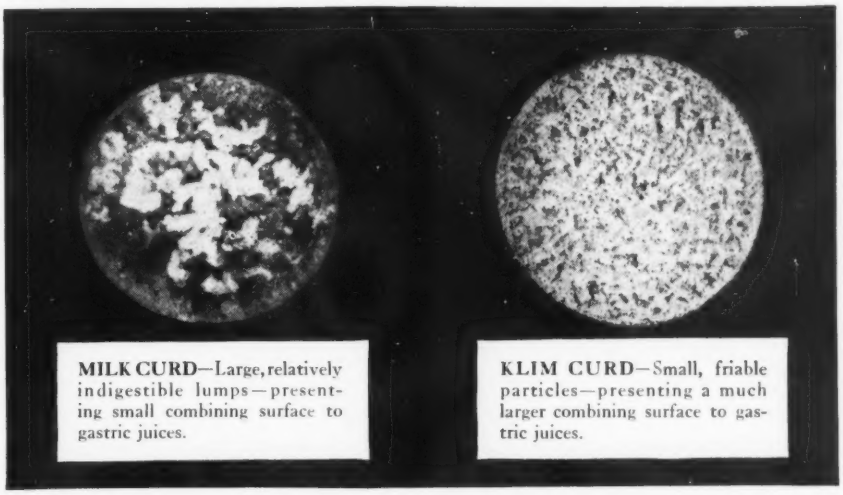
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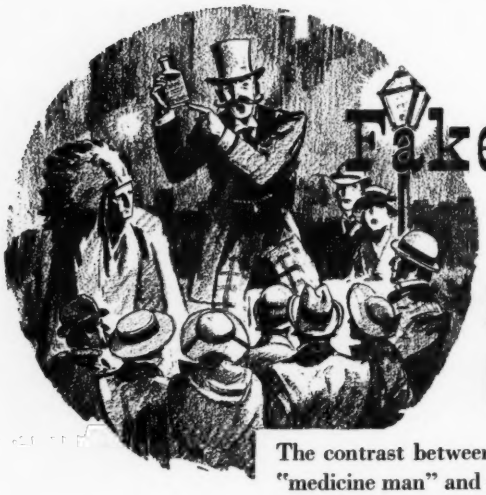

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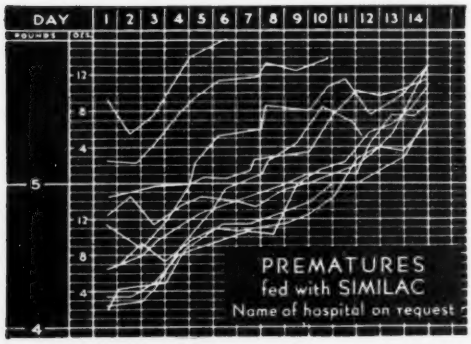

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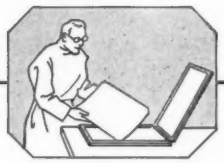

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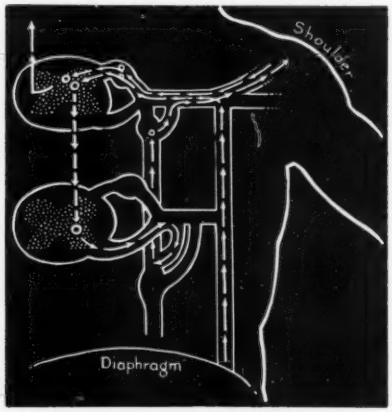

Schematic drawing showing the route of referred pain to the shoulder tip that originated in the diaphragmatic pleura.

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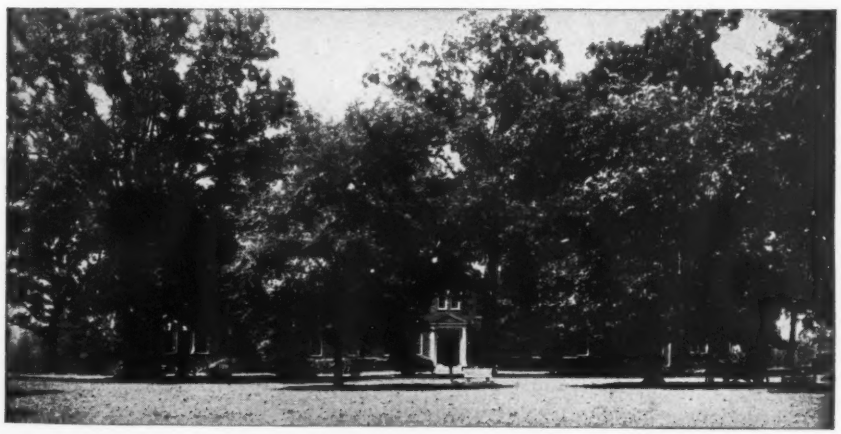

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Volume 30 MAY 1937 Number 5

EXPERIENCE WITH PROTAMINE ZINC INSULIN*

By M. R. WHITEHILL, M.D.
and
GEORGE A. HARROP, M.D.
Baltimore, Maryland

Protamine insulin was introduced in Denmark by Hagedorn and his associates, who announced its preparation about two years ago. During the past year it has been the subject of several very encouraging clinical reports.[1 2 3] We received supplies of the original material about a year and a half ago, and since then we have been actively engaged in studying its clinical value in diabetes. The present report is based upon a group of about forty patients who have been carefully studied. As is well known, the preparation to which zinc is added was first made available for clinical use in the summer of 1936. This is the material now marketed exclusively as protamine zinc insulin, and with the exception of one case (L. M.), all of the patients included in the present report have received this material since its introduction.

The physiological action of ordinary insulin is usually ended after about seven or eight hours, while that of the protamine zinc insulin lasts for at least twelve to twenty-four hours, and in all probability has a cumulative action for even longer periods. An important clinical advantage of the new preparation is held to be that it enables the number of necessary daily insulin injections to be reduced and that it increases their effectiveness. Of particular interest is the possibility of maintaining the blood sugar at physiological levels throughout the night. As is well known, in severe cases of diabetes it is often very difficult to secure a normal sugar value in the early morning even if an injection of insulin is given late at night. Unless the patient's renal threshold is very high in such cases, sugar usually also appears in the urine voided in the early morning.

Notwithstanding many of the enthusiastic reports which have appeared, our own preliminary studies with protamine insulin were disappointing. We naturally chose cases of maximum severity, in which, over a period of years, we had never quite secured satisfactory regulation with ordinary insulin. We found that we were no more fortunate in our efforts with the protamine than we had been previously. Various dietary regimes were used, and protamine insulin was given in one or two doses, alone or supplemented by injections of ordinary insulin. Further, we have had a number of very severe insulin reactions which differ in some respects from those seen with regular insulin. These are especially apt to occur when sufficient insulin is given to secure accurate regulation of the blood sugar over the entire day. The patients usually lapse into these insulin reactions gradually and often are almost unaware of them, although the peculiarities of their behavior may be apparent to the observer. Despite treatment by mouth, or even intravenous glucose, symptoms will sometimes persist. The absorption of food from the stomach is gravely impaired and the ingestion of quickly metabolized carbohydrate foods cannot surely be relied on to stop the attacks completely. Nervous manifestations are especially marked, and we have had a number of examples of transient hemiplegia and of localized convulsive seizures. Severe headache is experienced for several hours after such an attack. When headache is complained of upon arising in the morning, it is highly suggestive of an abnormally low blood sugar during the preceding night. We have also learned that patients taking protamine insulin who complain of drowsiness or mental dullness may really be suffering from such chronic hypo-

*Read in General Clinical Session, Southern Medical Association, Thirtieth Annual Meeting, Baltimore, Maryland, November 17-20, 1936.

*From the Chemical Division of the Medical Clinic, Johns Hopkins University and Hospital, Baltimore.

glycemia. As is well known, the blood sugar level at which clinical insulin reactions occur varies considerably, and we have had numerous instances in which the blood sugar concentration (capillary) has been 60 mgs. per cent or less over prolonged periods without evidence of symptoms. The consequences of maintaining the blood sugar for many hours or days consistenly below the normal physiological level are not known. It has been found experimentally to cause cerebral hemorrhages[29] and perhaps eventually cystic degeneration in the brains of dogs. The possibility of similar clinical effects must be borne in mind, if adequate studies of the blood sugar are not made. Estimation of the fasting blood sugar or of the blood sugar at one time during the day is not enough. The patients reported in this paper (with the exception of the few designated otherwise in the tables) have been studied over extended periods in the metabolism ward with

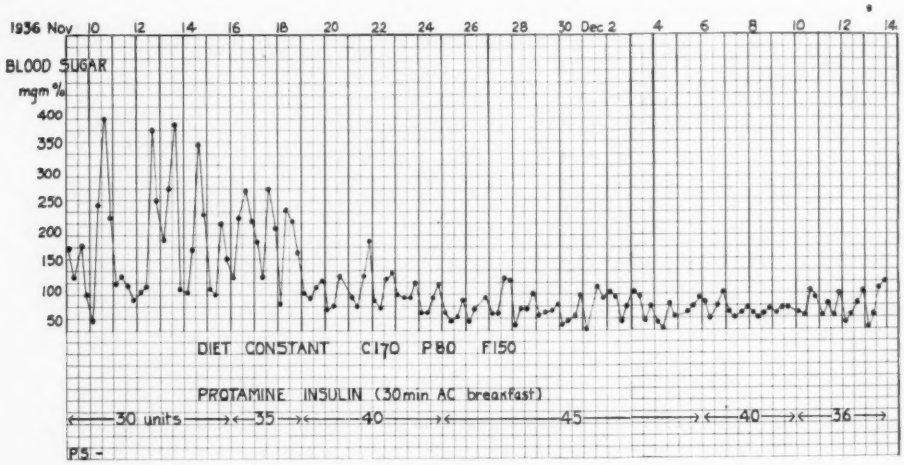

Chart 1

Patient regulated after two weeks of protamine insulin adjustment, apparently in a satisfactory way. However, on examination two months later, regulation was very bad, despite continuation of the prescribed regime.

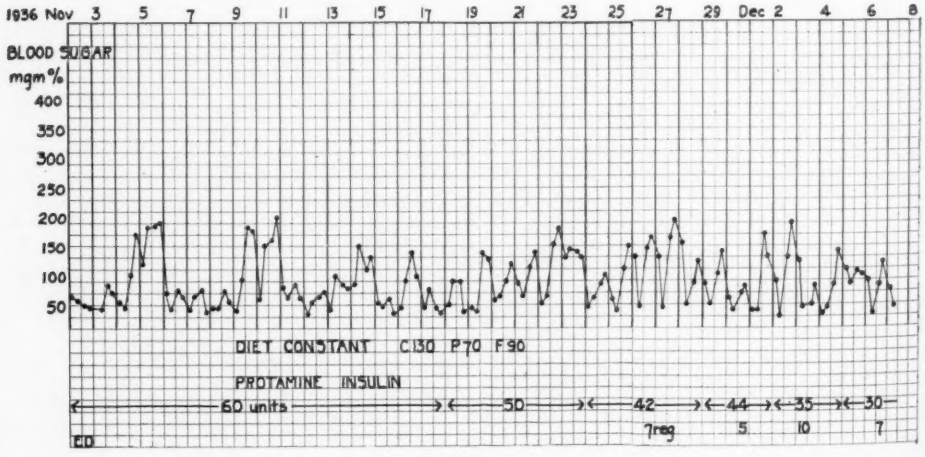

Chart 2

This chart indicates the wide fluctuation in blood sugar levels from day to day, in spite of constant regulation of food intake and insulin.

frequent blood sugar estimations throughout each day. In a number of cases this study was prolonged over a considerable period. At intervals during the subsequent observation outside the hospital, they have been readmitted for a day or two in order to check the blood sugar values throughout the course of twenty-four hours.

We have found, contrary to published reports, that the use of a single dose of protamine insulin is not feasible in many cases, even when food intake and insulin injections are accurately regulated. If continuous serial blood sugar estimations are made over the entire day, a curious cyclic effect is often observed, in which periods of hypoglycemia lasting from one to several days alternate with periods of hyperglycemia accompanied by the excretion of considerable amounts of urinary sugar (charts). The period in which the blood sugar is very low may cause the patient to complain of few symptoms, but if it is allowed to continue it may culminate in a severe insulin reaction. The cause of this disturbance is at present unknown and speculation will contribute little. Whether irregular absorption of protamine insulin may take place from the subcutaneous tissues under certain conditions has not, in the opinion of the writers, been clearly determined.

The clinical importance of clear recognition of this phenomenon in sensitive persons is quite obvious and the necessity for caution in regulating the protamine insulin dosage is evident. Thus if one were influenced during the periods of hyperglycemia and glycosuria into increasing the protamine insulin dosage instead of lowering it, as is really indicated, an aggravation of the condition is likely to result with severe reactions. We believe that the combination with regular insulin is more effective and generally safer than the use of very large single doses of protamine alone. Contrary to many observers, we hesitate to give single dosages of protamine zinc insulin in excess of thirty units at a time because of these cumulative effects. It is not possible to generalize regarding the number of units of protamine insulin required to regulate a given case as compared to the dosage for regulation with ordinary insulin. Some require more, others less. Those who do well on protamine insulin frequently require fewer units.

We have divided our cases into two groups: severe diabetics and milder diabetics. In general, the severe diabetics were younger patients who had not been well controlled, despite several doses of insulin daily. They seemed to develop acidosis easily. The milder diabetics were on an average older, but there were several young patients in this group, too. Previous regulation was usually well maintained on two doses of insulin a day.

We have classified our patients into four categories, which are numerically designated in the tables, and which indicate our appraisal of the ultimate value of the use of protamine insulin. Group 1 represents patients in whom the number of necessary doses of insulin throughout the day is reduced, with freedom from glycosuria, and with an improvement in the fluctuations of the blood sugar curve, as measured during the waking hours. We do not consider mere reduction of the number of doses, with relative freedom from glycosuria, as successful treatment, unless the blood sugar picture throughout the course of the day is also definitely improved. If one daily injection of protamine is substituted for one daily dose of regular insulin the blood sugar curve must show this regulation to be advantageous. Unless this aim is attained, the case is placed in Group 2. Group 3, unimproved,

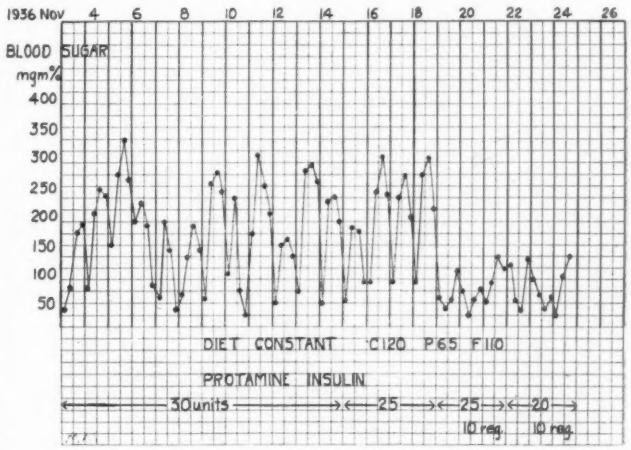

Chart 3

This indicates the wide fluctuations in blood sugar levels despite a constant therapeutic regime.

MILDER DIABETICS

	Name	Age	Sex	Duration of Diabetes	Most Effective Regular Insulin Regulation				Duration of Protamine Treatment	Most Effective Protamine Regulation			Classification of Patient, Group*	COMMENTS
					Diet C P F	Insulin (2)	Blood Sugar Curve (1)	Glycosuria		Dosage (2)	Blood Sugar Curve (1)	Glycosuria		
1	W.S.	21	M	5 years	140-70-120	20-0-11-0	173-104-123-132	+	7 months	15P-0-0-0 7R	66-72-100-99	+	1	Very low renal threshold
2	E.I.	23	M	2 years	140-60-100	18-0-11-0	147-94-130-98	0-+	7 months	11P-0-0-0 16R 15P-0-0-0	135-107-86-89 —70—	0 0	1	Returned to one dose of regular insulin as an experiment, but glycosuria appeared and protamine was resumed
3	J.B.	31	M	3 years	120-80-130	17-0-14-0		+	7 months	20P-0-0-0 10R	238-230-215-303	+	3	On the same and greater amounts of protamine and regular insulin regulation unsatisfactory
4	C.C.	25	M	6 years	120-70-135	13-0-8-5	120-90-270-132	+	1 year	25P-0-0-0 8R	68-82-160-152 —177—	+	3	Several severe reactions with protamine. Usually had moderate glycosuria and subsequent blood sugars high
5	L.M.	18	F	5 years	100-65-80	20-0-15-0	290—167—	+	4 months	15R-0-12P-0	87-110-170-105 220-167—180	+	3	Protamine discontinued
6	D.C.	16	M°	6 years	140-60-140	20-10-20-20	111-110-62-33	0	3 months	10P-0-15P-0	177-100-182-257	+	3	Regulation on regular insulin could have been improved
7	W.B.	40	M	5 years	100-70-110	10-0-10-0	182-164-192-159	0	3 months	18P-0-0-0	105-118-106-114	0	1	Patient feels better on protamine
8	E.Mk.	23	M	4 years	150-60-110	20-0-15-0	182-105-106-48	+	2 months	15P-0-0-0 14R	206-164-194-200	+	4	Mild diabetic, not responding to protamine
9	R.C.	29	M	3 years	120-70-140	20-0-18-0	145-50-95-60	0	7 months	14P-0-0-0	81-101-77-112	0	1	Mild diabetic, well controlled on one dose of protamine
10	F.S.	14	M	6 months	150-60-100				7 months	23P-0-0-0 12R 25P-0-0-0 10R	129-67-83-69 206-75-196-182	0 + (2 mos. later)	?	Not treated with regular insulin

(1) Capillary blood sugars taken before each meal and at 11:00 P. M.
(2) P = Protamine zinc insulin.
R = Regular insulin.
Insulin given before each meal and at 11:00 P. M.
*This classification represents an appraisal of the therapeutic effect of protamine insulin, as described in the text.

MILDER DIABETICS Continued

	Name	Age	Sex	Duration of Diabetes	Most Effective Regular Insulin Regulation				Duration of Protamine Treatment	Most Effective Protamine Regulation			Classification of Patient, Group*	COMMENTS
					Diet C P F	Insulin (2)	Blood Sugar Curve (1)	Glycosuria		Dosage (2)	Blood Sugar Curve (1)	Glycosuria		
11	E.Vs.	32	F	1 year	140-70-100				6 months	5P-0-0-0	111-133-94-152	0	?	No regular insulin, but an excellent response to protamine
13	C.T.	18	M	2 years	120-70-100	15-0-15-0	258-199-89-56	+	2 months	15R-10-15P-0	194-328-317-420	+	4	Much worse curve with protamine
14	C.H.	12	M	2 years	210-105-95	20-10-10-0	Well regulated	0	6 months	20P-0-0-0 5R	125-50-150-87	0	1	Protamine reduced to 10 subsequently
15	W.A.	46	M	10 years	120-70-120		270-200-240—	+	3 months	35P-0-0-0 10R	100-180-170-80	0 to +	1	This patient was treated in another hospital. Regulation on regular insulin could have been improved upon
16	C.D.	47	F	3½ years	140-70-80 100-65-70	10-0-10-0		0	4 months	26P-0-0-0 (later cut to 17P)	56-95-142-84	0 to +	2	The patient also had cirrhosis of the liver?, hemochromatosis, hypertension, and benign nephrosclerosis
17	B.E.	55	F	5 years	120-60-130	25-0-10-0 25-0-0-0	102-99-77-109 —119-102-118	0 0	6 months	5P-0-0-0 15R	—112—	0	2	Returned to regular insulin at own request. Reactions
18	W.R.	66	M	8 years	120-70-160 (high fruit)	12-0-6-0	109-92-121-118	0	5 months	28P-0-0-0	85-100-139-194	0 to +	3	Complained of irregularity. Mild reactions
19	B.K.	58	F	12 years	120-65-120	18-0-10-0	Usually had high A.M. sugar	+	5 months	21P-0-0-0 10R	83-149-133-179	+	2	A moderately severe case which was benefited by protamine insulin
20	G.T.	59	M	10 years	100-70-90	20-0-20-0	84-71-72-42	0	3 months	15P-0-0-0 16R	87-56-131-71	0	1	Fairly mild diabetes in middle aged patient who was improved by protamine
21	E.M.	45	F	12 years	110-60-90	25-0-10-0	141-145-112-137	0	3 months	15P-0-0-0 10R	143-145-102-168	0	1	Fairly mild diabetes successfully treated with protamine
22	P.S.	18	M	1½ years	170-80-150	23-0-17-0	118-54-105-58	0	6 months	36P-0-0-0	53-63-84-105 206-233-208-227	0 +	3	Second curve 2 mos. after first

(1) Capillary blood sugars taken before each meal and at 11:00 P. M.
(2) P = Protamine zinc insulin.
R = Regular insulin.
Insulin given before each meal and at 11:00 P. M.

*This classification represents an appraisal of the therapeutic effect of protamine insulin, as described in the text.

SEVERE DIABETICS

	Name	Age	Sex	Duration of Diabetes	Most Effective Regular Insulin Regulation				Duration of Protamine Treatment	Most Effective Protamine Regulation			Classification of Patient, Group*	COMMENTS
					Diet C P F	Insulin (2)	Blood Sugar Curve (1)	Glycosuria		Dosage (2)	Blood Sugar Curve (1)	Glycosuria		
1	C.G.	17	M	3 years	200-100-150	20-10-8-4	174-56-74-151	+	10 mos.	15R-5R-12P-0	127-83-56-105	+	3	Usually had moderate glycosuria with protamine. Finally developed severe acidosis
2	E.D.	19	F	4 years	130-70-90	38-0-29-0	263-139-194-52	+	4 mos.			0 to +	2	See chart
3	C.W.	14	M	5 years	200-60-85	10-0-8-0	106-73-101-103	0	5 mos.	46P-0-0-0 50P-0-6P-0	60-80-55-260 ——250-0-0	+	3	Cooperation poor
4	N.C.	33	M	12 years	185-50-150	27-0-18-5	196-65-123-48	+	10 mos.	25P-0-0-0	59-56-127-89	0	1	Patient feels he is greatly improved with protamine insulin
5	M.M.	37	F	5 years	120-65-110	30-0-10-20	215-80-135-55	+	1 year				3	Marked variations. Several bad reactions. See chart
6	W.B.	24	M	3½ years	164-131-165	20-18-0-0	187-125-102-100	?	3½ mos.	12P-0-24P-0 20R	157-72-74-167	+	4	Other protamine curves poor
7	C.T.	36	F	9 years	140-70-140	5-0-20-0 7-0-15-0	Well regulated 101-147-164-87	0	4 mos.	18P-0-0-0 6R	111-122-110-157	+	4	In general regulation not as good as curve indicates, so regular insulin resumed
8	I.K.	26	F	12 years	150-50-100	40-15-20-20	220-119-91-98	+	11 mos.	20R-6R-12R-12P	200-145-164-87	+	2	A severe diabetic subject to respiratory infections and diarrhea
9	M.K.	17	F	7 years	110-60-90	30-0-17-0 32-12-15-10	222-128-230-125 165-71-91-50	+ 0 to +	2 mos.	25P-0-5R-25P 5R	154-56-31-145	+	4	Numerous combinations of protamine and regular insulin were tried, but hyper and hypoglycemia were always present during the same day. Put back on regular insulin
10	V.D.	39	M	1½ years	125-70-155	30-10-25-5	160-108-194-155	0 to +	8 mos.	27R-0-14R-27P	142-138-84-58	0 to +	3	This patient also had hemocromatosis and finally died. Reactions were about as frequent with protamine as with regular insulin
11	R.E.	29	F	10 years	270-125-140 150-125-50	32-16-0-12 20-10-0-8	247-127-84-198 211-86-127-167	+ +	3 mos.	30P-0-18P-0	182-189-164-206	+	3	This patient also had fatty diarrhea osteoporosis, malnutrition and a general lowering of blood electrolyte values. Discharged on regular insulin because she lived out of town. Several severe reactions with protamine insulin
12	J.R.	41	F	10 years	60-60-90 130-90-65	14-0-16-0 10-8-10-10	120-64-144-123 195-149-165-270	0 to + +	4 mos.	22R-0-15R-12P	108-171-198-148	+	4	This patient also had rheumatic heart disease and diarrhea. These curves do not represent a true account. On protamine, hyperglycemia and insulin reaction were frequent. Regulation has been more constant and satisfactory on regular insulin resumed after four months.
13	J.R.	47	M	6 years	100-80-100	20-0-20-0	412-45-115	+	5 mos.	30P-0-0-0 10R	215-234-228-278	+	3	Heavy glycosuria and reactions on protamine
14	E.P.	38	F	13 years	100-60-100	30-0-20-0	225-130-93	0 to +	8 mos.	25R-0-20P-0	145-62-78-63	0 to +	2	Voluntarily returned to regular insulin

(1) Capillary blood sugars taken before each meal and at 11:00 P. M.
(2) P = Protamine zinc insulin.
R = Regular insulin.
Insulin given before each meal and at 11:00 P. M.
*This classification represents an appraisal of the therapeutic effect of protamine insulin as described in the text.

is self-explanatory. We have had several examples of Group 4 in which a return to the use of ordinary insulin proved to be of definite advantage.

The findings are summarized in the charts which indicate the efficiency of treatment on regular insulin alone, prior to the use of protamine zinc insulin. The results with the latter then represent what we have considered the most efficient method of administration for the particular individual. In each instance various doses of protamine zinc insulin alone and combined with regular insulin and various food combinations were tried.

COMMENT

The encouraging reports which have appeared regarding the value of protamine insulin and protamine zinc insulin in the treatment of diabetes indicate clearly that it constitutes a therapeutic advance of genuine importance. Nevertheless, we are unable to confirm unreservedly, on the basis of our own experience, all of the advantages which others have found. It is difficult to make many generalizations from the present study, although on the whole better results have been obtained in the milder cases. The most serious drawback to the use of protamine zinc insulin as compared to ordinary insulin in the treatment of some individuals, we think, lies in its prolonged and not always predictable action. Care is needed in order to avoid recurrent insulin reactions. Protamine zinc insulin is by no means an innocuous therapeutic agent which can be prescribed with relative disregard of consequences. Patients who are not cooperative and who are lax in the management of their diet, in our experience do badly. Individuals with moderately severe diabetes who will not submit to a careful regular dietary regime, will find the use of regular insulin safer and on the whole more satisfactory.

The variable effect upon the blood sugar, as shown in the charts, in which periods of hypoglycemia may alternate with periods of hyperglycemia must be emphasized. This may occur with or without frank clinical manifestations. We think this effect is not rare and that examples will undoubtedly come to light more frequently whenever extended studies are made of the blood sugar curve in a given patient throughout the course of a number of days. The effect is more common with the prolonged use of large doses of protamine alone, but it also occurs when the combination is used.

On the whole, our experience with protamine zinc insulin in the treatment of very severe diabetes or in diabetes with serious complications, such as diarrhea, has not led us to believe that it is usually of significantly greater value than is ordinary insulin, and where variability of food absorption occurs it is not as safe. Protamine zinc insulin is of particular value in milder cases in which two or three doses of ordinary insulin may be replaced by one dose, either alone or combined with a simultaneous injection of regular insulin. Frequently, although not invariably, the blood sugar is maintained at a more normal level.

To summarize our findings, we feel that a considerable experience will be required in order to appraise satisfactorily the place of protamine zinc insulin in diabetic therapy. A number of our patients have benefited greatly. We cannot now predict with assurance, in advance, its clinical value for any given patient. Further study will no doubt clarify many of the present problems.

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*Insulin given before each meal and at 11:00 P. M.
**This classification represents an appraisal of the therapeutic effect of protamine insulin as described in the text.

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THE RESULTS OF A COUNTY-WIDE SURVEY AND AN OUTLINE OF THE SYPHILIS CONTROL PROGRAM IN GIBSON COUNTY, TENNESSEE*

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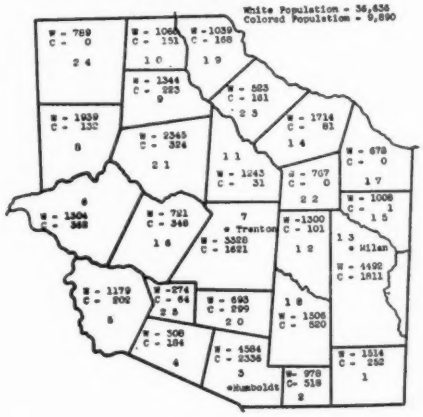
Gibson County is situated in the western part of Tennessee with its western boundary about thirty miles from the Mississippi River. The land is slightly rolling with some low hills in the eastern section. A great part of the county is composed of lowlands which are traversed by drainage ditches that have reclaimed thousands of acres for agriculture. The average altitude is about 400 feet. The total area is approximately 650 square miles.

The county is essentially agricultural and is said to be second in the United States in the diversification of crops. In 1929, the value of farm products in Gibson County was in excess of $8,000,000. There are one cotton mill, one oil mill, two canning factories, three box factories, several flour mills, and other small manufacturing plants in the county, but the chief industry is farming.

According to the 1930 census, the population of the county was 46,528, of which 9,890 were colored. The rural farm population was 30,501, with 5,367 persons listed as rural non-farm. There are eight incorporated towns in the county with populations varying from 500 to 4,500.

The county is divided into political subdivisions, twenty-five civil districts, all of which are about equal in size. *Fig. 1* shows the civil districts, the population of these districts by color, and the three largest towns. It will be noted that Districts 3, 7 and 13 have the greatest population. These are the only urban districts in the county. The colored population is fairly well scattered over the county, but there are five districts with less than fifty Negroes in each.

FIGURE 1
GIBSON COUNTY, TENNESSEE--CIVIL DISTRICTS AND POPULATION BY DISTRICT AND COLOR



Gibson County established a full-time county health department in 1922; the first syphilis clinic was started in 1925. The program was endorsed by the county medical society and no patient is admitted to the clinic for treatment without a written reference from a physician. Only eight persons were admitted to the syphilis clinic in 1925 and by 1929 there had been 275 cases under treatment. From 1925 through 1935, 893 cases of syphilis were discovered and approximately 40,000 individual treatments given in the three clinics operated by the county health department.

The reporting of syphilis by physicians in the

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county has been poor, but when it is considered that approximately 90 per cent of all cases are treated and reported by the health department, this apparently poor reporting is better understood. The physicians seem to feel that referring a case to the health department clinic is the same as reporting it. *Table 1* shows the reporting of cases of syphilis by physicians and by clinics and the total cases under treatment by years in the county since 1929.

Early in 1935, at a conference between officials of the Commonwealth Fund and the State and county health departments, it was decided to make a syphilis and malaria survey of Gibson County. Considerable publicity was given to the malaria aspects of the survey in order to prevent stigmatization of the entire project. The purpose of the survey was two-fold: first, we wanted accurate base-line data as to the prevalence of syphilis in the general population so

Table 1

CASES REPORTED, CASES ADMITTED AND TOTAL CASES UNDER TREATMENT
GIBSON COUNTY, 1929-1935

	1929	1930	1931	1932	1933	1934	1935	Total
New cases admitted	132	266	264	116	107	143	152	1180*
Reported by physicians	20	24	9	6	8	13	2	82
Reported by clinic	127	231	308	130	113	175	164	1248
Cases under treatment	227	319	316	316	235	268	254	1935

*This number represents data taken from annual reports and includes new admissions and patients admitted who later were discharged with a change of diagnosis.

Table 2

POPULATION, NUMBER AND PERCENTAGE OF PERSONS EXAMINED FOR SYPHILIS, NUMBER AND PERCENTAGE OF POSITIVE REACTORS FOUND BY COLOR AND CIVIL DISTRICT
GIBSON COUNTY, TENNESSEE

	Population			Number Examined						With Three Plus or Better on One or More Tests					
				White		Colored		Total		White		Colored		Total	
Civil Dist.	White	Colored	Total	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
1	1514	252	1766	135	8.92	49	19.44	184	10.41	1	0.74	0	0	1	0.55
2	978	518	1496	106	10.84	67	12.93	174	11.56	1	0.94	9	13.43	10	0.58
3	4584	2336	6920	559	12.19	260	11.13	819	11.83	7	1.25	18	6.92	25	3.05
4	308	184	492	56	18.18	15	8.15	71	14.43	1	1.79	2	13.33	3	4.22
5	1179	202	1381	162	13.74	37	18.31	199	14.41	5	3.09	8	21.62	13	6.53
6	1304	362	1666	344	26.83	42	11.60	386	23.17	2	0.58	3	7.14	5	1.29
7	3328	1621	4950	474	14.24	172	10.61	646	13.05	9	1.90	10	5.81	19	2.94
8	1939	132	2071	166	8.56	10	7.57	176	8.49	7	4.22	0	0	7	3.97
9	1344	223	1567	142	10.56	51	22.87	193	12.32	0	0	3	5.88	3	1.55
10	1066	151	1217	101	9.47	55	36.42	156	12.82	3	3.00	9	16.36	12	7.69
11	1243	31	1274	179	14.40	21	67.74	200	15.69	1	0.56	1	4.76	2	1.00
12	1300	101	1401	126	9.69	60	59.40	186	13.27	1	0.79	0	0	1	0.54
13	4492	1811	6304	509	11.33	233	12.87	742	11.77	4	0.78	18	7.72	22	2.96
14	1714	81	1795	152	8.87	36	44.44	188	10.47	1	0.66	6	16.66	7	3.72
15	1008	1	1009	69	6.84	0	0	69	6.83	1	1.44	0	0	1	1.44
16	721	348	1069	89	12.34	53	15.23	142	13.28	1	1.12	2	3.77	3	2.11
17	678	0	678	65	9.59	0	0	65	9.59	1	1.54	0	0	1	1.54
18	1506	520	2026	188	12.48	95	18.26	283	13.97	3	1.59	3	3.16	6	2.12
19	1039	168	1207	87	8.37	58	34.52	145	12.01	2	2.30	4	6.89	6	4.14
20	693	299	992	109	15.73	16	5.35	125	12.60	1	0.92	0	0	1	0.80
21	2345	324	2669	215	9.16	96	29.63	311	11.65	5	2.32	6	6.25	11	3.54
22	767	0	767	52	6.78	1	0	53	6.91	0	0	0	0	0	0
23	523	161	684	57	10.89	24	14.91	81	11.84	1	1.75	5	20.83	6	7.41
24	789	0	789	120	15.20	0	0	120	15.20	1	0.83	0	0	1	0.83
25	274	64	338	35	12.77	5	7.81	40	11.83	0	0	1	—	1	2.50
	36636	9890	46528	4297	11.73	1456	14.72	5753	12.36	59	1.37	108	7.42	167	2.90

that progress of our syphilis control activities could be measured (although a fairly intensive clinic service had been maintained for ten years, there were no available data by which a comparative study could be made of the prevalence of syphilis in 1925 and 1935); second, we wanted to know where these cases were so that additional control measures could be inaugurated. Since blood samples were going to be taken, it was decided to examine each specimen for the presence of malaria parasites, the reaction to the Kahn and Wassermann tests and for the presence of agglutinins of tularemia, undulant fever, and proteus OX19. The entire program received the endorsement of the county medical society before any work was done. The field work was supervised by the Director of the Gibson County Health Department. A sampling group of approximately 10 per cent of the total population of the county, properly allocated by age, sex, color and civil district, was prepared before any specimens were collected. All physicians in the county were most cooperative during the entire survey. In several instances, centers for the collection of specimens were held in physicians' offices. (This discussion will be limited to the findings in the syphilis survey.)

A representative sample of the population was obtained. As will be seen from *Tables 2* and *3A* and *3B*, both colors, both sexes and all ages in all civil districts were examined. Since the blood test was presented as a "malaria test," there were very few refusals. People of all classes were examined. Doctors, lawyers, preachers, teachers, housewives, farmers, merchants, factory workers, tenant farmers, clerks and sharecroppers were included in the survey. There are no private schools in the county and all economic groups are represented in the school population.

Nearly all the specimens were obtained by the special nurse in charge of the collection of specimens with all workers in the county health department assisting in some way at various times.

In order to secure specimens the survey was well publicized. All newspapers in the county carried items concerning the plan of the study and places of examination. Women's clubs, lay health committees, service clubs and community clubs were addressed by various workers. Factory superintendents were consulted. Collection centers were announced in churches, in the schools and at all public gatherings. Many centers were held in or near country stores, churches and schools. The home demonstration agent of the county aided in organizing several centers among the various community clubs. Where there was only one physician in a community, the center was located in his office.

Blood specimens were collected in sterile syringes which had been rinsed in sterile saline. A thick smear of the blood was made on a glass slide from part of the blood in the syringe. The remainder of the blood was then placed in a sterile vial. The slide and vial were numbered for identification and wrapped together with the laboratory slip which had been prepared in duplicate. The laboratory slip provided space for identification of the donor, the worker collecting the specimen, the time the specimen was collected, mailed, and received in the laboratory and a report of laboratory results. Both slips were sent with the specimen, the results were recorded in

Table 3-A

NUMBER OF PERSONS EXAMINED, NUMBER AND PERCENTAGE OF POSITIVE REACTORS FOUND BY AGE, COLOR AND SEX
GIBSON COUNTY, TENNESSEE

Age	Number Examined				Number Positive				Percentage Positive			
	White		Colored		White		Colored		White		Colored	
	M	F	M	F	M	F	M	F	M	F	M	F
0- 4	67	53	44	44	3	1	2	5	4.48	1.89	4.55	11.36
5-14	647	741	273	270	5	5	9	17	0.77	0.67	3.29	5.55
15-24	415	558	139	191	9	11	9	20	2.17	1.97	8.47	10.47
25-44	472	672	153	159	3	10	15	14	0.63	1.34	9.80	6.92
45+	302	370	93	90	8	4	10	7	2.65	1.08	9.67	7.78
Total	1903	2394	702	754	28	31	45	63				

Table 3-B

NUMBER EXAMINED BY AGE AND DISTRICT

District Number	0-4		5-14		15-24		25-44		45-64		65 Plus		Total	
	W	C	W	C	W	C	W	C	W	C	W	C	W	C
1	3	4	37	12	33	8	35	11	21	11	6	3	135	49
2	2	2	47	48	26	9	21	6	6	0	4	2	106	67
3	17	17	125	56	120	49	199	101	78	29	20	8	559	260
4	3	2	22	1	10	3	15	8	4	0	2	1	56	15
5	7	3	70	10	32	10	31	8	18	4	4	2	162	37
6	17	4	163	15	92	7	42	9	22	4	8	3	344	42
7	9	6	92	67	100	45	156	33	90	15	27	6	474	172
8	3	1	44	0	43	0	41	5	27	4	8	0	156	10
9	2	7	46	18	35	8	32	10	20	5	7	3	142	51
10	9	5	22	21	18	12	29	15	16	1	7	1	101	55
11	11	1	68	7	25	3	50	3	19	4	6	3	179	21
12	3	5	33	34	35	17	37	3	14	1	4	0	126	60
13	5	14	188	78	146	69	138	48	28	20	4	4	509	233
14	1	0	43	13	29	12	46	7	29	4	4	0	152	36
15	3	0	39	0	17	0	13	0	6	0	1	0	79	0
16	7	4	28	33	22	4	23	8	7	1	2	3	89	53
17	1	0	34	0	8	0	12	0	9	0	1	0	65	0
18	9	2	54	52	42	24	46	7	23	8	4	2	178	95
19	1	2	19	15	22	21	25	11	14	8	6	1	87	58
20	1	1	42	6	22	6	26	1	15	2	3	0	109	16
21	4	6	60	45	46	15	62	13	36	11	7	5	215	95
22	0	0	21	0	11	0	15	0	5	1	0	0	52	1
23	1	2	16	11	15	7	15	3	8	1	2	0	57	24
24	1	0	69	0	15	0	20	0	12	0	3	0	120	0
25	0	0	16	1	9	1	5	2	4	1	1	0	35	5
Total	120	88	1398	543	973	330	1134	312	531	135	141	48	4297	1456

Note: Population 0-4, 4616.
Population 65 and over, 2461.

the laboratory, one slip retained by the laboratory and the other mailed back to the field.

The cubital veins were used for securing most of the specimens, but in very young children the external jugular was used.

Some of the specimens were iced and sent to the laboratory, but it was soon found that this was a cumbersome and expensive method. Nearly all of the specimens were placed in the centrifuge in the local health department office and the serum sent to the laboratory. In very hot weather these sera were iced. All specimens were mailed the same day that they were collected except when this would cause the specimens to remain too long in transit. On weekends the sera were kept on ice in the health department office and mailed in time to reach the State laboratory early Monday morning.

Some difficulties were encountered and some mistakes were made. The greatest difficulty encountered was that of securing enough specimens from children under 5 and from adults over 65 years of age. *Table 3A* shows that this difficulty was not entirely overcome. It will be noted that only 7.7 per cent of the population over 65 years of age and 4.6 per cent of the population under 5 years of age had blood tests.

One of the mistakes made was failure to include in the address, the exact location of the person with reference to some school, store, church, or other landmark. The postoffice address was not always sufficient to locate these

persons requiring a re-examination. Another mistake was failure to record on children's records the name of the head of the family. Vacuum tubes, in lieu of syringes, would have facilitated the collecton of specimens.

Table 2 shows the sample was a representative sample and that every district in the county was represented (in the survey) both as to color and sex. *Tables 3A* and *3B* show that all age groups were represented, and as has been pointed out earlier, all classes of people were included.

Table 3A shows the results of the Kahn and Wassermann tests by age, color and sex. *Fig. 2* shows these results graphically. An initial three-tube Kahn was routinely run on all specimens and a cholesterolized antigen Wassermann was run on all positive Kahns. Only those specimens showing a three-plus or stronger Kahn or Wassermann or both were classified as positive.

In both races and in both sexes the rates from 0 through 4 years of age were higher than in the following ten years. These rates are based on relatively small numbers and are perhaps less reliable than the rates for the next older age group. If the age group, 0-14, is compared with the 15-24 age group, the rates are as shown in *Table 4*.

Table 4

SYPHILIS PREVALENCE BY COLOR, SEX AND AGE
GIBSON COUNTY, TENNESSEE

	White		Colored	
Age	Male	Female	Male	Female
0-14	1.12	0.75	3.47	7.00
15-24	2.17	1.97	6.47	10.47

Assuming, however, that the rates for the 0 to 4 year group are reliable, there is a real difference* between these rates and those for the age group 5 to 14. Maxcey and Brumfield[1] found a syphilis rate of 3.8 per cent in the 0 to 9 age group and 3.4 per cent in the 10 to 14 age group. If our sample is adequate for the 0 through 4 year group, the most logical explanation of the difference is that the serum reaction in congenital syphilis tends to become negative with time. Jeans and Cook[2] found a prevalence of 2.4 per cent in white infants and 9.3 per cent in colored infants. Wenger,[3] studying colored children in Pitt County, North Carolina, found that 3.0 per cent of the children under 5 years of age had syphilis. Except the study of Jeans and Cook, which was done on hospital registrants, we know of no studies of the general white population.

In the age group, 5 to 14 years (*Table 5*) the rate for the colored was slightly higher than the rate of 4.6 which Wenger found for the same age group in Pitt County, North Carolina, and markedly lower than the rate of 9.7 found by Crabtree and Bishop[4] in Tipton County, Tennessee. The rate of 4.78 per cent for Gibson County was somewhat higher than the rate of 3.5 found by Maxey and Brumfield in Albemarle County, Virginia.

The rates of 2.17 per cent for white males and 1.97 per cent for white females from 18 to 24 years of age are much higher than the 0.2 per cent found by Diehl[5] for white college students. The prevalence rate of syphilis among the general population of white females from 18 to 44 years of age in Gibson County was 1.71 per cent as compared to the rate of 0.9 per cent found in 1,368 pregnant white women of the same age group in Gibson County.

After 45 years of age, the rate becomes slightly lower in colored males and white females and slightly higher in colored females. On the basis of data at hand, there is no real difference in

*$\frac{X}{\infty} = 2.8$.

Table 5

COMPARISON OF FINDINGS OF THE GIBSON COUNTY SURVEY WITH OTHER SURVEY DATA

Age	Gibson County Survey				Univ. Minn.	Albemarle County	Tipton County	Pitt County	Pregnant Women Gibson County	
	White Female	White Total	Colored Female	Colored Total	White	Colored	Colored	Colored	White	Colored
5-14	0.77	.72	5.55	4.78	—	3.5	9.7	4.6	—	—
15-24	1.97	2.05	10.47	8.79	0.2	10.7	17.3	16.3	0.71	8.5
25-44	1.34	1.13	6.92	9.29	—	19.3	40.6	15.3	1.06	9.26
45 plus	1.08	1.78	7.78	9.29	—	11.9	23.6	10.4	—	—

these rates. The prevalence rate in white males over 45 is significantly higher than the rate for the age group, 25 to 44. We have no explanation to offer for this phenomenon.

Table 5 shows the findings in the Gibson County survey compared with those in other areas. With reference to the white population, there are really no comparable figures, but those found by Diehl working with college students and those found in Gibson County in pregnant women are listed.

Except for the 5 to 14 age group (*Table 5*) the rates among the colored population in Gibson County are lower than those found in Pitt County, North Carolina, and Albemarle County, Virginia, and much lower than those found in Tipton County, Tennessee.

Table 6 shows the distribution of syphilis by geographical areas in the county. Realizing that district boundaries are highly artificial, districts were grouped together into nine areas.

It will be seen that the rates differ from area to area, but there are no real differences and the cases of syphilis may be said to be uniformly distributed over the county. The colored rate is very much higher than the white rate, a fact which has been noted by all workers.

The prevalence of syphilis for white females in Gibson County is 1.21 per cent, for white males 1.53 per cent, for colored females 8.33 per cent, and for colored males 6.58 per cent.

In so far as possible the survey was limited to the non-clinic population, that is, patients who had been previously examined in the venereal disease clinics were not included in the survey. Occasionally a person was examined at the survey clinic who had been in the venereal disease clinics. There were forty-six such cases, but not enough to change the result. Thirty-three of the forty-six were found to be non-syphilitic in the clinic and in the survey. One colored female was positive in both clinic and survey. Two colored females were found to have syphilis in the survey who had been found negative several years before in the venereal disease clinics. Five colored males, two white males, one white female and two colored females were negative on the survey findings, but one had been in the venereal disease clinics and had been treated for syphilis. *Table 7* shows the number of persons examined in the syphilis clinics of the county since 1930, the number and percentage of these registrants who were syphilitics. It will be noted that prior to the survey there were 111 cases of syphilis known in the white population and 507 cases in the colored population.

The survey resulted in the finding of 111 white and 56 colored cases that were unknown, unreported, and untreated.

If the survey rates are reliable, and we have

Table 6

NUMBER OF PERSONS EXAMINED. NUMBER AND PERCENTAGE OF CASES OF SYPHILIS FOUND BY GEOGRAPHICAL AREAS, SEX AND COLOR GIBSON COUNTY, TENNESSEE

District	Number Examined				Cases Found				Prevalence Percentage			
	Male		Female		Male		Female		Male		Female	
	White	Col.	White	Col.	White	Col.	White	Col.	White	Col.	White	Col.
1,2	107	51	139	65	2	2	0	7	1.87	3.92	0	10.77
3,4	316	152	294	122	6	12	2	9	1.89	7.89	0.68	7.37
5,6,16	253	61	335	71	3	3	5	10	1.19	4.91	1.49	14.08
7,20,25	275	88	343	105	2	5	8	6	0.73	5.68	2.33	5.71
8,11,21	253	69	307	58	8	3	5	4	3.16	4.34	1.63	6.89
9,10,24	165	54	198	52	2	8	2	4	1.21	14.81	1.01	7.69
12,13,18	323	176	500	212	4	10	3	11	1.24	5.68	0.60	5.18
14,15,17,22	140	16	198	21	0	1	3	5	0	6.25	1.51	23.80
19,23	62	32	82	50	2	2	1	7	3.22	6.25	1.22	14.00
Total	1894	699	2396	756	29	46	29	63	1.53	6.58	1.21	8.33

Table 7

NUMBER OF CLINIC REGISTRANTS, NUMBER AND PERCENTAGE OF CASES OF SYPHILIS FOUND BY AGE, COLOR AND SEX

GIBSON COUNTY, 1930-1935, INCLUSIVE*

Ages	Clinic Registrants				Cases Syphilis Found				Percentage Syphilitic				Total Rate	
	White		Colored		White		Colored		White		Colored			
	M	F	M	F	M	F	M	F	M	F	M	F	Wh.	Col.
0- 4	15	10	33	33	1	0	2	6	6.66	0	6.06	18.18	4.00	12.12
5-14	39	47	111	159	1	3	8	21	2.56	6.38	7.21	13.21	4.65	10.74
15-24	200	99	444	471	21	22	81	149	10.50	22.22	18.24	31.63	14.38	25.40
25-44	277	162	402	385	34	15	98	104	12.27	9.26	24.38	27.01	11.16	25.67
45+	95	41	133	98	10	4	28	10	10.54	9.76	21.05	10.20	10.29	16.45
Total	626	359	1123	1146	67	44	217	290	10.70	12.26	19.32	25.31	11.27	22.34

*In comparing with Table 1, note that Table 1 includes readmissions and Table 7 includes only individuals.

no reason for thinking they are not, there are at least 495 cases of syphilis in the white non-clinic population of the county and when to this are added the 111 known cases of syphilis from the clinic population there is a total of 606 white cases, or a rate of 1.69 per cent. On the same basis there are 565 cases in the non-clinic Negro population, which, with the 507 known cases in the clinic population, makes a total of 1,072 cases, or a prevalence rate of 10.8 per cent.

The Commonwealth Fund and the State Department of Health have set up a budget for the follow-up of these cases. A nurse is to be added to the staff of six nurses, including the nursing supervisor, now in the county. The follow-up program in cases of early syphilis will be identical with the procedure for handling other acute communicable diseases except that quarantine will be resorted to only for the control of delinquent cases. All contacts are to be included in the follow-up program.

The budget provides for arsenicals and bismuth to be given to all of the physicians in the county for treatment of these cases and all others that can be found. The health department will establish three additional clinics for the treatment of cases referred by the physicians.

Extra funds for travel have been assigned to the medical staff of the department for epidemiological investigations of early cases.

In all cases where the nurse has a family folder on a family where there is a case of syphilis, a record of this will be placed in the folder and when the case lapses, in taking treatment, this fact will be noted on the record and the nurse can urge the return to the clinic.

SUMMARY

(1) The study has demonstrated that a syphilis survey of a general rural population can be made without unusual difficulty.

(2) A representative sample comprising 11.7 per cent of the white and 14.7 per cent of the colored population in Gibson County, Tennessee, was examined serologically for syphilis. The survey findings, together with the clinic group, gave a syphilis prevalence rate of 1.69 per cent and 10.8 per cent for the white and colored populations, respectively.

(3) The feasibility of having one person directly responsible for the collection of specimens was, in our experience, satisfactorily demonstrated.

(4) Although an intensive diagnosis and treatment service has been carried on for approximately ten years, the survey figures indicate that at least 58 per cent of the syphilis cases in Gibson County were *unknown, unreported, and untreated.*

(5) Cases counted as positive in the survey were only those that showed 3+ or stronger on one or more serological tests. All positive Kahns were checked by a single antigen Wassermann.

(6) It is reasonable to expect that the follow-up program to cases classified as positive and doubtful cases as well will increase the case rate of both races.

(7) An intensive educational program reaching high school groups, civic and lay organizations and the medical profession is being conducted prior to the intensive follow-up program.

(8) Cases and contacts are to be handled as

Table 8

NUMBER AND PERCENTAGE OF SYPHILITICS IN GIBSON COUNTY WHEN 2 PLUS TESTS ARE ADDED TO THE 3 PLUS TESTS. FIGURES IN THE PARENTHESES ARE THE 3 PLUS TESTS

Districts	Male				Female			
	White		Colored		White		Colored	
1, 2	3	(2)	2	(2)	1	(0)	7	(7)
3, 4	8	(6)	15	(12)	3	(2)	11	(9)
5, 6, 16	4	(3)	5	(3)	8	(5)	13	(10)
7, 20, 25	3	(2)	7	(5)	17	(8)	11	(6)
8, 11, 21	9	(8)	3	(3)	10	(5)	4	(4)
9, 10, 24	4	(2)	9	(8)	5	(2)	6	(4)
12, 13, 18	6	(4)	16	(10)	5	(3)	14	(11)
14, 15, 17, 22	1	(0)	2	(1)	3	(3)	6	(5)
19, 23	2	(2)	3	(2)	1	(1)	9	(7)
Totals	40	(29)	62	(46)	53	(29)	81	(63)
Rates (%)	2.11	(1.53)	8.87	(6.58)	2.21	(1.21)	10.71	(8.33)

any other acute communicable disease in the control program that is being instituted.

(9) The data collected in this survey will serve as a yard-stick for measuring the progress of the future control program.

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DISCUSSION (*Abstract*)

Dr. I. C. Riggin, Richmond, Va.—It is quite difficult of course to discuss the measures employed in making this survey. Nevertheless, I think we are agreed that it is necessary for similar surveys to be conducted if adequate control programs are to be instituted. I shall not attempt to discuss the statistical findings or facts as brought out in this paper. The reason for my not discussing this aspect of the presentation, I am sure, is evident to all.

To me the most interesting conclusion to be drawn is the need for additional epidemiological work by the county health officers on each case of venereal disease reported. I feel that we have been negligent in this respect. If we are to have an adequate venereal disease control program, it is just as essential that epidemiological procedures be carried out in relation to venereal diseases as for other communicable diseases. We must know the contacts, the probable source of infection, and other pertinent epidemiological factors.

Only through more intensive epidemiological investigations can we hope to develop a successful venereal disease control program.

THE EVALUATION OF SERODIAGNOSTIC TESTS FOR SYPHILIS UPON THE SPINAL FLUID*

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At the suggestion of the American Society of Clinical Pathologists the United States Public Health Service sponsored investigations to determine the reliability of serodiagnostic methods used in the United States upon both the blood and the spinal fluid. A committee consisting of two syphilologists, two clinical pathologists, and one officer of the Public Health Service was appointed by the Surgeon General of the Service to organize and conduct the evaluation study. This work has been completed and published.[1]

Samples of the spinal fluid were sent to:

Walter V. Brem, Los Angeles, California.

Harry Eagle, Philadelphia, Pennsylvania.

F. M. Johns, New Orleans, Louisiana.

Reuben L. Kahn (performing Kahn standard diagnostic test), Ann Arbor, Michigan.

B. S. Kline (performing Kline diagnostic test), Cleveland, Ohio.

John A. Kolmer, Philadelphia, Pennsylvania.

M. B. Kurtz (performing Kahn presumptive test), Lansing, Michigan.

N. H. Lufkin and F. Rytz, Minneapolis, Minnesota.

Charles R. Rein (performing Kline exclusion test), New York, New York.

E. Henry Ruediger, San Diego, California.

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Emil Weiss, Chicago, Illinois.

Capt. W. C. Williams (U. S. Army), Washington, District of Columbia.

Drs. Brem, Kolmer, and Ruediger, and Captain Williams performed complement-fixation tests. All the other participants performed flocculation tests. Although Dr. William A. Hinton, of Boston, participated in the blood examination, he did not perform any tests upon the spinal fluid.

Donors were carefully chosen and accurate records were made of the important facts of the history and of the physical findings upon examination. As much care as possible was taken to insure that they be available for clinical re-examination in the event that discrepancies appeared in the reports of the participating serologists. The donors comprised 101 cases of dementia paralytica, 8 cases of diffuse cerebrospinal syphilis, and 1 case of myelitis. Spinal fluid specimens were collected under aseptic conditions directly into uniform glass tubes. In addition one hundred and ten spinal fluid specimens were taken from presumably nonsyphilitic patients. Each of these specimens was divided into 12 comparable samples, of which each participating serologist received a sample containing at least 3 c. c. A total of 2,640 samples was collected and of these 99 were not satisfactory for examination. It is interesting to note that there were but two participating serologists upon the Pacific coast, and these two men reported 71 instances where the tubes were received in an empty condition, or where the sample was not satisfactory. These samples were chiefly sent by air mail, and it has been suggested that the high altitude at which the planes flew was responsible for the corks' being forced out because of the lower air pressure on the outside of the tubes. This phase of work will be the subject of a later report.

EVALUATION OF SPECIFICITY AND SENSITIVITY

1.—The sensitivity and specificity of tests were graded by their ability to detect or exclude syphilis in spinal fluid specimens from neurosyphilitic patients and from presumably nonsyphilitic patients with other mental diseases. When the doubtful reports are given no consideration the results are good with the exception of two of the complement-fixation tests, and two of the flocculation tests. If the serologists are penalized for doubtful reactions, only the tests of Brem, Eagle, Kurtz, Kline, Rein, and Kolmer show more than 99 per cent of specificity. It should again be emphasized that doubtful reports are not evaluated in the published statistics, inasmuch as neither the Committee nor the participating serologists was able to decide what value should be given to them. It should further be mentioned that the results of the tests did not arouse a suspicion of the presence of neurosyphilis in any patient in this group.

2.—The specificity of blood and spinal fluid tests for syphilis was studied based on the percentage of negative reports on all presumably nonsyphilitic donors, and contrasted with the sensitivity of blood and spinal fluid tests for syphilis based on the percentage of positive reports on syphilitic donors. In four instances the percentage of sensitivity is lower in the tests upon the spinal fluid than in the tests upon the blood.

The percentage of sensitivity among most of the serologists is less than a syphilologist would expect in dementia paralytica. This has led to an intensive investigation for the reason thereof. It has been learned that the percentage of positive reactions upon patients who either had received no treatment, a very small amount of treatment, or unsuitable treatment, was very much higher than in the patients who had been treated with either tryparsamide or malaria. Fewer than 12 injections of tryparsamide are considered to be inadequate. Mercury or bismuth injections alone are considered unsuitable. Fewer than 15 injections of arsphenamine, at proper intervals, are likewise considered inadequate. *Table 1* will show the figures upon this group of 39 patients. The Committee believes that the fairest way to judge the sensitivity of the tests in patients suffering from dementia paralytica is upon serum from those who have had neither tryparsamide nor malaria. Three of the flocculation tests are unsatisfactory as regards sensitivity even in this group of patients. It is only fair to note that Johns states that 5 c. c. of spinal fluid are needed for his test, and that the samples which he received contained but 3 c. c.

DISAGREEMENT AMONG SEROLOGISTS

There was far more disagreement upon individual patients whose spinal fluid was examined than upon individual patients submitted to blood examination. In searching for an explanation the effects of malaria therapy were examined. *Table 2* shows the degree of disagreement among the serologists. This table also shows the degree

Table 1

SENSITIVITY OF SPINAL FLUID TESTS IN 39 NEUROSYPHILITIC PATIENTS WHO HAD RECEIVED LITTLE OR NO TREATMENT

Serologists	Total Specimens Examined	Doubtful Reports	Positive Reports	Percentage of Positive Reports Penalized for Doubtful Reports	Percentage of Positive Reports Not Penalized for Doubtful Reports	Percentage of Positive Reports (Doubtful Reports Excluded from Total)
Brem[1]	36	—	33	91.7	91.7	91.7
Eagle	38	—	37	97.4	97.4	97.4
Johns	39	—	21	53.8	53.8	53.8
Kahn	39	1	38	97.4	100.0	100.0
Kline	37	—	36	97.3	97.3	97.3
Kolmer[1]	37	1	31	83.8	86.5	86.1
Kurtz[2]	39	2	37	94.9	100.0	100.0
Lufkin & Rytz	39	1	28	71.8	74.4	73.7
Rein[3]	39	2	36	92.3	97.4	97.3
Ruediger[1]	36	—	36	100.0	100.0	100.0
Weiss	39	—	34	87.2	87.2	87.2
Williams[1] (Army)	39	1	38	97.4	100.0	100.0

1. Performed modification of complement fixation tests.
2. Performed Kahn presumptive test.
3. Performed Kline exclusion test.

All others performed flocculation tests.

Note.—Little treatment is here defined as less than 12 injections of tryparsamide or less than 15 injections of arsphenamine.

of agreement or disagreement in patients who had been treated with induced malaria, and patients who had received no malaria treatment. It will be seen that patients who had been treated with induced malaria presented a much higher degree of disagreement than did those who had not received such treatment. *Table 3* shows the percentage of positive, negative, and doubtful reactions in the total number of syphilitic patients whose fluid was examined, and the influence of malaria treatments. There is a much higher percentage of negative reactions among those who have had malaria therapy. This high percentage of negative results exists even when those participating serologists did not obtain satisfactory results.

COMPLEMENT-FIXATION VERSUS FLOCCULATION TESTS

Table 4 shows the difference in the results obtained by the flocculation tests and by the complement - fixation tests. Complement - fixation tests taken by and large are more sensitive than are flocculation tests when applied to the spinal fluid. However, certain of the flocculation tests are superior to some of the complement-fixation tests. A study of *Table 1* reveals the fact that

Table 2

DEGREE OF AGREEMENT OR DISAGREEMENT AMONG SEROLOGISTS ON THE RESULTS OF SPINAL FLUID TESTS IN NEUROSYPHILITIC PATIENTS WHO HAD HAD INDUCED MALARIA AND IN THOSE WHO HAD NOT HAD THIS FORM OF THERAPY

Degree of Agreement or Disagreement Among Serologists	Total Specimens Examined		Induced Malaria		No Malaria Therapy					
					Total		No Treatment, or Less than 12 Injections of Tryparsamide or Less than 15 Injections of Arsphenamine		12 or More Injections of Tryparsamide or 15 or More Injections of Arsphenamine	
	No.	%	No.	%	No.	%	No.	%	No.	%
No. on which all agreed	36	32.7	6	17.7	30	39.5	17	43.6	13	35.1
No. on which 1 disagreed	23	20.9	3	8.8	20	26.3	11	28.2	9	24.3
No. on which 2 disagreed	16	14.5	6	17.7	10	13.2	4	10.3	6	16.2
No. on which 3 disagreed	7	6.4	1	2.9	6	7.9	4	10.3	2	5.4
No. on which 4 disagreed	4	3.6	2	5.9	2	2.6	—	—	2	5.4
No. on which 5 disagreed	5	4.6	1	2.9	4	5.3	1	2.6	3	8.1
No. on which 6 disagreed	3	2.7	2	5.9	1	1.3	—	—	1	2.7
No. on which 7 disagreed	5	4.6	5	14.7	—	—	—	—	—	—
No. on which 8 disagreed	6	5.5	3	8.8	3	3.9	2	5.1	1	2.7
No. on which 9 disagreed	3	2.7	3	8.8	—	—	—	—	—	—
No. on which 10 disagreed	1	.9	1	2.9	—	—	—	—	—	—
No. on which 11 disagreed	1	.9	1	2.9	—	—	—	—	—	—
Total	110	100.0	34	99.9	76	100.0	39	100.1	37	99.9

Table 3

A COMPARISON OF THE RESULTS OF SPINAL FLUID TESTS MADE IN NEUROSYPHILITIC PATIENTS WHO HAD HAD INDUCED MALARIA AND IN THOSE WHO HAD NOT HAD THIS FORM OF THERAPY (BASED ON SAMPLES, NOT PATIENTS)

Reactions	Total Specimens Examined		Induced Malaria		No Malaria Therapy					
					Total		No Treatment, or Less than 12 Injections of Tryparsamide or Less than 15 Injections of Arsphenamine		12 or More Injections of Tryparsamide or 15 or More Injections of Arsphenamine	
	No.	%	No.	%	No.	%	No.	%	No.	%
Positive reactions	1009	79.2	237	61.4	772	86.9	405	88.6	367	85.2
Negative reactions	220	17.3	125	32.4	95	10.7	44	9.6	51	11.8
Doubtful reactions	45	3.5	24	6.2	21	2.4	8	1.8	13	3.0
Total	1274*	100.0	386*	100.0	888	100.0	457	100.0	431	100.0

*Exclusive of 1 anticomplementary reaction.

Table 4

A COMPARISON OF THE TOTAL NUMBER OF SPINAL FLUID SPECIMENS EXAMINED BY THE FLOCCULATION AND COMPLEMENT-FIXATION METHODS, THE NUMBER AND PERCENTAGE OF POSITIVE REPORTS IN NEUROSYPHILITIC PATIENTS, AND THE NUMBER AND PERCENTAGE OF FALSE POSITIVE REPORTS IN PRESUMABLY NONSYPHILITIC PATIENTS WITH OTHER MENTAL DISEASES

Type of Spinal Fluid Test	110 Neurosyphilitic Patients			110 Nonsyphilitic Patients		
	Total Specimens Examined	No. of Positive Reports	Percentage of Positive Reports	Total Specimens Examined	No. of False Positive Reports	Percentage of False Positive Reports
Flocculation test	867	653	75.3	870	17	2.0
Complement-fixation test	408	356	87.3	396	9	2.3
Total	1275	1009	79.1	1266	26	2.1

3 of the flocculation tests rank well below either the remaining flocculation tests or the complement-fixation tests. If these 3 tests are excluded, there is very little difference between the sensitivity of the complement-fixation and the flocculation tests. Obviously it is of the utmost importance that the selection of tests for the spinal fluid be made most carefully.

NEGATIVE REACTIONS

The study of *Table 3* shows that from patients not treated with malaria 888 samples of spinal fluid were obtained and that of these 86.9 per cent were positive. Practically all of these patients had dementia paralytica.

The general understanding among syphilologists is that practically all untreated patients with paralytica should show a positive serological reaction in the spinal fluid (Horgan,[3] Hazen,[4] Nonne,[5] Fordyce and Rosen,[6] McIntosh, Fildes, Head and Fearnsides,[7] and Stokes[8]).

That the spinal fluid may be negative in some cases of cerebrospinal syphilis had been reported by Moore,[9] who states that in about one-half of the cases of cerebrospinal syphilis under treatment the fluid will show a negative reaction.

Solomon and Klauder[10] report that in tabes dorsalis the fluid of patients under treatment often becomes negative. Many other observers agree with these views.

LITERATURE

There have been many reports concerning the effects of malaria upon the spinal fluid, which have been well summarized by Vonderlehr.[11] Hinsie and Blalock[12] report that the Wassermann reaction upon the spinal fluid became negative in 83.1 per cent of patients treated with malaria. Osborne[13] reported 29 per cent of approximately 400 mixed cases of neurosyphilis. O'Leary and Brunsting,[14] examining the status of patients three to five years after treatment, found the spinal fluid completely negative in 52 per cent of 60 cases, and markedly improved in an additional 30 per cent. Moore[15] reported that 55 per cent of cases of dementia paralytica show both clinical and serological improvement. Grant[16] stated that the spinal fluid Wassermann was not affected until a later period, but was then considerably changed. Fong and Ferraro[17] found no relationship between clinical and serological improvement. Finger and Kyrle[18] and Kyrle[19] insisted that malaria therapy produced marked improvement in spinal fluid findings. Pisani[20] believes that clinical and laboratory signs of improvement ran hand in hand. Nicole and Fitzgerald[21] noted that the fluid improvement after malaria was most marked some four or more years after treatment. Grosz and Straussler[22] observed that the Wassermann reaction upon the spinal fluid usually remained positive despite clinical remissions. Should the remission be of long duration the spinal fluid Wassermann might also become negative. Hombria and Enterria[23] reported that the Wassermann reaction in the fluid is remarkably persistent, and that changes in it bear little relationship to clinical changes.

DISCUSSION

It is obvious that a test for syphilis of the nervous system must possess both specificity and sensitivity. Of necessity any figures are purely arbitrary. However, examination of the spinal fluid is most frequently performed in known cases of syphilis, so a little leeway as regards specificity is not as serious a matter as a lack of specificity in a test applied to the blood serum. As regards specificity it is probable that the test should rate at least 99 per cent. It is to be noted that Moore[24] uses this figure as applied to blood serology. As regards sensitivity the test should rate at least 90 per cent. The rating of the participating serologists is modified if they are penalized for doubtful results in their specificity figures, and rewarded for them in their sensitivity figures. If there is no penalty for doubtful reports the following tests are satisfactory as regards specificity: Brem, Eagle, Kahn presumptive test, Kahn standard test, Kline exclusion test, Kline standard test, Kolmer, and Lufkin and Rytz. If these tests are penalized for doubtful reports the Kahn standard test and the Lufkin and Rytz test fail to qualify by a narrow margin.

As regards sensitivity, it would seem that the figures should be based upon patients who have received no malaria, or less than 12 injections of tryparsamide, or less than 15 injections of arsphenamine. The tests qualifying for sensitivity are those of Brem, Eagle, Kahn (both tests), Kline (both tests), Ruediger, and Williams (United States Army). If sensitivity be rated upon the well treated, poorly treated, and untreated cases of neurosyphilis, the qualifying tests are the Kahn standard and the Ruediger tests with the Brem and Kline diagnostic tests barely failing.

There are several of the flocculation tests which are not suitable for spinal fluid examination. If these are excluded, there is no choice between flocculation and complement - fixation tests. The majority of laboratory technicians prefer a test which, with certain slight modifications, can be safely employed for both blood and spinal fluid specimens.

The amount of disagreement among the serologists is much greater upon patients treated with malaria or tryparsamide than upon patients but slightly treated, or untreated.

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DISCUSSION (*Abstract*)

Dr. Harry M. Robinson, Baltimore, Md.—This work of which Dr. Hazen's paper is the result was undertaken with the idea of determining the relative efficacy of the several technics employed for the detection of syphilis of the central nervous system, and one must deduce after hearing the conclusions that it is important not only to do serologic tests on the blood and spinal fluid, but that only such tests should be employed as are known to have a high level of sensitivity and specificity. The authors have shown that all tests are not applicable to the spinal fluid. I wish to ask Dr. Hazen if he does not think the words "doubtful" and "positive" as such are inadequate, and whether for the fuller determination of the patient's condition from a diagnostic and prognostic standpoint, it would not be wiser to test the spinal fluid quantitatively. It should be further emphasized that while the serologic test on the cerebrospinal fluid is the only one which is absolutely specific for syphilis, nevertheless the examination of the cerebrospinal fluid is incomplete and often misleading unless it includes also a cell count, quantitative protein estimation and a colloidal test (gold, mastic or benzoin). It is only with a corollary of all these tests that one can give an impression of definite value on the basis of which the proper treatment can be instituted. Finally, I wish to emphasize that every syphilitic should be urged to have a spinal fluid examination; patients with primary syphilis after the first few months of treatment and the patients with latent or late syphilis during the first two or three visits. In the event of a positive reaction, immediate adequate treatment will give the patient at least 90 per cent greater hope of complete recovery.

Dr. R. A. Vonderlehr, Washington, D. C.—A rare opportunity is offered at this time to express both to Dr. Hazen and to the other members of our Committee on Evaluation of Serodiagnostic Tests for Syphilis the gratitude of the Public Health Service for the cooperation and interest which these physicians have shown in this series of important studies.

Naturally, I am in complete agreement with Dr. Hazen. I feel that the point which he brings out with regard to the use of donors of spinal fluid who have syphilis of the central nervous system and who have not been treated with induced malaria is most important in the evaluation of sensitivity. This is particularly true in the evaluation of serologic tests on the spinal fluid which are employed primarily for diagnostic purposes. When serologic tests are used to determine the progress which has been made as the result of the application of treatment in central nervous system syphilis, the results of such tests should be correlated with the results of the other tests which are frequently used when the spinal fluid is examined. Recent work of the Cooperative Clinical Group soon to be published has also demonstrated the value of classifying the spinal fluid findings into four arbitrary groups as soon as a diagnosis of central nervous system syphilis has been made. The use of such a system permits of a more accurate determination of the prognosis in such patients.

It should be particularly noted that the evaluation of serodiagnostic tests here reported on spinal fluid includes only the most recently developed and efficient tests. The comparisons made, therefore, should be of the greatest assistance to both the specialist and the physician. It is likewise to be hoped that the demonstrated efficiency of the better serodiagnostic tests here described will act as a deterrent in the routine adoption of other serologic procedures of unknown efficiency.

Dr. Charles R. Rein, New York, N. Y.—The disparity of results with the various tests for the detection of syphilis in spinal fluids is quite striking. One would certainly expect such a dissimilarity in treated cases with varying amount of treatment. In these cases one would expect the less sensitive tests to be negative, while the more sensitive tests would remain positive for a longer period of time, accounting for some of this difference. The disparity in results, however, in the untreated cases is quite discouraging. It is also important to evaluate the doubtful reactions more carefully. In the absence of a suggestive history or symptoms, a doubtful reaction should not be used to stigmatize the patient as having syphilis of the central nervous system. It is important, however, to respect doubtful reactions in spinal fluids from individuals with histories or symptoms suggestive of central nervous system syphilis. In such instances a doubtful reaction is of definite value, indicating the necessity for repeated spinal fluid examinations at more frequent intervals until a definite diagnosis can be made. In this evaluation study the specimens examined were identified by number only so that the serologist had no knowledge of the clinical status of the individual. In clinical practice, however, it is important that the serologist work in cooperation with the clinician and that he be furnished with all the clinical data available. In this manner a more accurate interpretation of serologic results could be made.

It might also be worth while in future studies of this type to include spinal fluids from patients with meningitis, encephalitis and other nonspecific diseases of the

central nervous system. This would increase the number of controls of non-syphilitics which may be used to evaluate the specificity of each test.

Dr. Hazen (closing).—This study is a beginning, which simply represents the evaluation of the qualitative tests as applied to the spinal fluid. In no sense does it deny the value of quantitative tests.

The Committee feels that the serum was obtained in the only practicable way, namely, from definitely non-syphilitic, hospitalized cases. Considering the large amount of serum needed, it would have been more than difficult to persuade 110 normal individuals to furnish this amount.

OX-FASCIA-TRANSPLANT OPERATION FOR PTOSIS*

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There are three possible ways by which ptosis may be corrected: first, one may increase the action of the levator muscle. Second, one may elevate the lid by utilizing the upward movement of the eyeball; there are a variety of methods for attaching the lid to the eyeball. Third, in certain cases one must use the power of the frontalis muscle. There are cases in which not only the action of the levator muscle is entirely lacking, but in addition the patient cannot raise the eyes. A new method of dealing with this type of ptosis is herewith introduced.

There are a number of methods of attaching the lid to the frontalis muscle, but most of them are of historical interest only. Fascia lata seems to be the logical material with which to make the connection between the lid and brow: it is very strong and lasting; it is not a foreign body; and it does not induce lid deformity. The only serious disadvantage in the use of this material is that to obtain it an operation on the leg is required.

To eliminate this disadvantage the writer has recently used ox fascia, prepared and marketed in a sealed glass ampule. This material was introduced by Amos Koontz, of the Department of Surgery of the Johns Hopkins University Medical School, who has used it extensively in hernia repair. The fascia is sterilized after being removed from the animal and is preserved in the ampule in alcohol. The ampule is opened before the operation and the fascia washed in physiological saline. The strip is about eight inches long and usually rolls out into a flat piece about one inch wide. The surgeon can cut or tear a small narrow strip of suitable size for work on the lid, and it seems in use to be the same as human fascia.

The operation performed by the writer is probably similar to that used by many other surgeons. For those unfamiliar with it, the various steps in the operation are described together with a few refinements introduced by the writer. If the patient is old enough, one should use nerve-block anesthesia. It is helpful to have the cooperation of the patient so that the surgeon may know exactly how much correction he has obtained during the operation. With infiltration anesthesia there is so much swelling of the lids that lid movements are hindered and the deformity makes it impossible for the surgeon to judge accurately the degree of correction he has obtained. For these reasons the choice of anesthesia is very important. The frontal nerve, the infratrochlear nerve and the lacrimal nerve are concerned in this operation.

The surgeon begins by making a one-centimeter transverse incision in the center of the upper lid at the level of the upper border of the tarsus. A similar incision, one centimeter long, is made directly above the first and about one to two centimeters above the brow. The first incision should be carried down to the tarsus; the second incision should be made deep through the thick skin of that region. The next step is to pass the fascia needle (Reverdin) from the lower incision to the upper incision. (In the absence of this instrument, a long, curved cutting needle can be used in its place.) The needle passes into the wound to the level of the tarsus, thence upward and slightly backward, so that the needle point will strike against the roof of the orbit on the inside of the bony rim. By forcing the needle to this position one has made it pass behind the orbitopalpebral fascia. This layer is fairly thick at its periosteal origin. The needle is now advanced forward and upward, perforating the orbitopalpebral fascia, and is passed on and out through the wound above. A narrow strip of fascia (at least three to four inches long and about one millimeter wide) is attached to the eye of the needle and drawn through the channel. The needle is detached from the fascia and placed again in the lower wound, three to four millimeters to one side of the original channel, and again passed upward toward the upper wound in exactly the same manner as before.

*Read in Section on Ophthalmology and Otolaryngology, Southern Medical Association, Thirtieth Annual Meeting, Baltimore, Maryland, November 17-20, 1936.

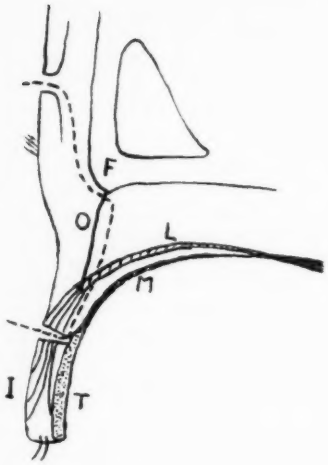

Fig. 1

Diagram of sagittal section through frontal region. Dotted line shows course of transplant. F, frontal bone; O, orbitopalpebral fascia; L, aponeurotic tendon of levator muscle; M, Muller's muscle layer connecting tarsus to levator muscle; T, tarsus; I, method of insertion of levator tendon into lid.

This time a heavy silk thread should be brought down and after being tied to the lower end of the fascia strip, should be pulled back up to the upper wound. In this way the fascia forms a loop with the two ends emerging from the upper wound. The lower end is looped through the deep tissue at the level of the upper border of the tarsus, giving a firm attachment for the fascia and making unnecessary the use of sutures at this point. The lid wound can then be closed with silk.

Before anchoring the upper part of the fascia it is well to form a pocket by undermining the lower lip of the wound. The two ends of the fascia are then tied in a simple knot on themselves and a suture of white silk is tied around the fascia knot which is to lie in the above mentioned pocket. At this stage the function of the lid should be tested. The patient is directed to follow the surgeon's finger as it is moved in different directions; the patient should also be asked to close his eyes as in normal sleep. If the tension on the transplant is not great enough, the fascia knot can be tightened; and conversely, if the tension is too great, the knot can be loosened. When the proper tension has been found, the thread is tied a second time, and is then passed as a suture through the loose ends of the fascia and tied again immediately above the knot. This makes a firm anchor, which is required, since fascia will slip very readily. The ends of the fascia are cut about one centimeter above the knot and are buried under the skin in a channel formed above the upper wound. The skin is then closed with silk. A pressure dressing is applied for 48 hours, and the sutures of the skin are removed on the third or fourth day. If the pressure dressing has been properly placed, there will be no swelling when the dressing is changed.

In children, as the face grows the distance between lid and brow will increase, but the transplant will not lengthen. The result would be an increase in the effect of the operation. Therefore, in operations on small children a slight undercorrection is to be preferred.

The tissue reaction to ox fascia is not different to that noted when human fascia is used. In fact, throughout the operation it is difficult to realize that human fascia is not being used. After healing has occurred one can feel the narrow bundle under the skin crossing the rim of the orbit. It is possible to judge the tensile strength of the transplant by holding the lid down with one finger and pulling up at the upper wound with the other hand.

According to Koontz, the prepared fascia behaves very much like the human-fascia transplant. In the case of the human transplant the living cells of the fascia die and the framework that remains is made of collagen, which is the same or nearly the same as in animal fascia.

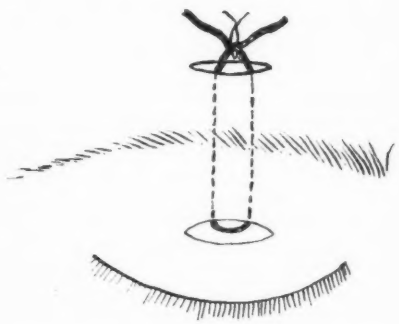

Fig. 2

Anterior view of lid showing fascia in place and suture looped around fascia knot.

This framework is invaded by fibroblasts which thereby make it a part of the host. In the case of the prepared fascia the collagen fibrils are unaltered in the preserving method. The material becomes organized and later made a part of the host as in the autogenous transplant.

COMMENT

This operation shows several advantages. The external wounds are very small and leave no scars. Anesthesia by nerve blocking allows an end result to be obtained at the operating table. The transplant material is easily obtained and behaves like an autogenous graft. By the use of the orbitopalpebral fascia as a pulley, the pull is directed sufficiently backward so that the lid will remain against the eyeball by capillary attraction and will not be lifted above the eye as a hat is raised. If both sides are involved, it is possible to perform one operation at a time and the patient can remain ambulatory.

823 Metropolitan Building

REFERENCE

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DISCUSSION (*Abstract*)

Dr. Amos R. Koontz, Baltimore, Md.—As I am a general surgeon and not an ophthalmologist, I shall make no attempt to discuss Dr. Hildreth's operation as an eye operation, but shall limit my remarks to some of the biological considerations underlying the use of ox fascia. Dr. Hildreth has already hinted at these in his paper. The theoretical basis for the use of this material is as follows: the collagen fibrils of the connective tissues are inert, intercellular substances, and are not alive in the sense that living protoplasm is alive. The preservation of these fibrils in alcohol does not change them either chemically or physically, as the connective tissue fibrils of catgut are changed in the course of its preservation, physically by the use of heat and chemically by the use of such chemicals as chromic acid or iodine. When the alcohol is washed out of the preserved ox fascia with salt solution, the collagen fibers are then just as they were when they were taken out of the animal, without any alteration whatsoever. When implanted in the host, new cells wander in from the surrounding tissues and repopulate the implanted fibers, fibroblasts and blood vessels grow in, and soon the implanted fascia is a living part of the organism into which it is implanted. There is no leukocytic or round cell reaction, as in the case of catgut or kangaroo tendon, and hence no tendency to absorption.

The question has come up as to why an implant from a different species does not cause a reaction on the part of the host and interfere with the "taking" of the graft. The answer to this is that alcohol destroys antigen and that, therefore, one does not get the foreign protein reaction that might be expected if a piece of living ox fascia were implanted in another species.

When my first paper on the use of ox fascia was published in 1926, its use was advocated for hernia repair, and the material has been extensively used for this purpose with excellent results. However, it has been used for a number of things besides this, namely: in the operation for recurrent dislocation of the shoulder; as a suture material in fracture cases; bands have been successfully used to encircle the fragments of broken femurs in Paget's disease, after plating had been unsuccessful; the material has been used for suspension of the vaginal vault, to cure prolapse following panhysterectomy; Stone has used it successfully in his operation for complete incontinence of feces; and it has also been used to supply defects in tendons. I now welcome the new use which Dr. Hildreth has given the material.

Dr. J. Wesley McKinney, Memphis, Tenn.—To those of us who like to do plastic work about the eye the use of ox fascia in place of the autogenous transplant of fascia lata has been a welcomed development. It is welcomed by the ophthalmic surgeon, because it greatly simplifies the procedure. It is welcomed by the patient, because it gets away from the leg operation. Many people, especially old men, complain bitterly of the sore leg following the removal of fascia lata.

I should like to present the procedure that I like to use. It varies only in minor details from the operation that Dr. Hildreth has just presented. It does further simplify the procedure.

The fascia strip is first sutured just behind the eye of a long curved cutting needle to prevent slipping during passage of the fascia through the tissues. A horizontal incision one centimeter long is made through skin and superficial fascia about one centimeter above the eyebrow. A stab wound is made in the skin one centimeter above this. Two stab wounds are made just below the upper margin of the tarsus and one centimeter apart. The fascia strip is passed from the upper incision beneath the skin of the brow and lid and out the corresponding stab wound in the lid; beneath the skin of the lid and out the other stab wound; and thence beneath the skin of lid and brow and out the upper incision. The fascia strip is tied and sutured so as to draw the lid up to the desired position. The two ends of the fascia are then passed beneath the skin and out the stab wound above the incision. The fascia is cut off so that the ends will be well below the skin surface. It is important that the fascia loop be broad in order that there may be no tenting of the lid margin.

This operation for ptosis is, of course, only to be used when the superior rectus is weak or inactive. By attaching the lid to the superior rectus a much better functional result is obtained. For this Dr. C. Allen Dickey, of San Francisco, has recently advocated a fascia sling to connect the tarsus and the superior rectus. This seems to be an improvement over the Motais operation. Ox fascia might be used here instead of fascia lata.

NEWER METHODS OF DIAGNOSIS AND TREATMENT OF THYROID DISEASE*

By DAVID HENRY POER, M.D., F.A.C.S.
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In general it may be said without arbitration that many practitioners of medicine have come to consider the diagnosis and treatment of thyroid disease fairly well standardized, and consequently have devoted little attention to the many reports and presentations that appear on this important subject. There may be some slight justification for this when one considers the rather low mortality rate reported in practically all of the large clinics which represents a striking reduction from the pre-iodine days before 1922. But mortality is not the only consideration in the treatment of a disease, and morbidity and differential diagnosis are still important factors so far as the average patient is concerned. During the past few years several important contributions have aided us to lower our percentage of error even more, and it is with these developments that we are concerned today.

The diagnosis of endemic goiter of diffuse or nodular type is usually without difficulty, and in itself presents no problem. Likewise primary hyperthyroidism of a moderate or severe grade is quite obvious. However, the correct management of even these simple forms of goiter frequently depends upon an accurate estimation of the severity of the symptoms and degree of hyperthyroidism from other conditions that present much the same symptomatology.

During the years past many of us have depended almost entirely upon the estimation of the basal metabolic rate, that is, measurement of the amount of oxygen consumed under given conditions. Perhaps in altogether too many instances it has been the sole determining factor in directing the treatment of a patient; if the basal rate was increased the patient had goiter (hyperthyroidism) and was treated for this even to the point of an operation; and contrarily, if the reading was normal the thyroid could not be the cause of the trouble.

Beginning about ten years ago, several observers began to point out the fallacy of this reasoning, and to cite examples of errors in diagnosis. Roger Morris[1] presented evidence that hearts damaged by thyroid activity occur in individuals in whom the basal metabolic rate has never been elevated, as if that part of the secretion of the thyroid that damaged the circulation was not necessarily a part of the substance which controlled the basal metabolic demands. More recently Gordon and Graham[2] and Davison[3] observed patients with normal or low basal readings, but with definite evidence of hyperthyroidism which was substantiated by typical improvement following removal. Further metabolic studies in many disease conditions and under various physical conditions have demonstrated increased readings, so that our faith in the basal test as an accurate estimation of thyroid activity has been considerably shaken. In fact so much so that many observers now place a reliance upon other tests such as blood iodine determination and cholesterol level, equal to or above that placed upon the basal metabolic rate.

The first determinations of iodine in the tissues were made by Kendall in 1914,[4] but it was ten years later that a satisfactory method was discovered for estimation of iodine in organic material by von Fellenberg[5] and McClendon.[6] Practically all workers in this field now use a modification of the test as described by von Fellenberg and later modified by McCullagh,[7] but the correct manipulation of the technic is still beset by many difficulties so that only a few special laboratories have been able to carry it out successfully. While much has been done to simplify the test, particularly by Perkin,[8] it still requires further modification before it will achieve the universal usage that is needed to demonstrate its value in diagnosis. The tests for our clinic have been done in the Department of Biochemistry at Emory University under the direction of Dr. George Lewis.

The normal human thyroid contains about 10 mg. of iodine at a concentration of 40 mg. per cent of wet weight. This may be markedly decreased in patients with hyperthyroidism due to a decrease in the amount of organic iodine, but at the same time the amount of blood iodine increases. The normal value for blood iodine is approximately 10 micrograms per 100 c. c. of blood; this figure is somewhat lower than that originally set down by Curtis and others, and may require further modification as our experience grows. The chemical basis for the test is the separation of the organic (hormonal) and inorganic (nutritional) fractions by precipita-

*Read in Section on Surgery, Southern Medical Association, Thirtieth Annual Meeting, Baltimore, Maryland, November 17-20, 1936.

*From the Emory University School of Medicine.

Table 1

COMPARISON OF BLOOD IODINE VALUES WITH BASAL METABOLIC RATES IN CASES WITH NO EVIDENCE OF GOITER

Case	Diagnosis	Basal Metabolic Rate. Per Cent	Blood Iodine Micrograms
35114	Congestive heart failure	+ 28	12.7
35100	Psychosis	— 12	9.73
35411	Arterial hypertension	+ 15	10.45
36023	Ovarian dysfunction	— 15	8.34
35115	Arterial hypertension	+ 18	11.5
35097	Hypogonadism	+ 5	7.3
35165	Anterior dyspituitarism	+ 7	12.09
		Average	10.3

tion with alcohol. The blood specimen is reduced to an ash and colorimetric titration done using sodium thiosulfate to bring out the starch iodine reaction.

In the following tables are shown blood iodine values in comparison with basal metabolic rates in a variety of conditions. In *Table 1* are a group of patients with conditions not related to surgical thyroid disease; the average level is approximately the same as that of normal individuals (10 micrograms).

In *Table 2*, the figures are given for a group of patients with a simple form of goiter without evidence of toxicity. In some of these patients there were definite clinical manifestations of hypothyroidism and this was further borne out by low basal rates and low iodine levels. The average for this group is somewhat higher than the normal (15 micrograms), and we believe this was caused by including several patients with high basal readings and high iodine levels who probably should have been included in the hyperthyroid group. They were not put in this group on account of absence of clinical evidence of hyperthyroidism.

Table 3 shows iodine values and basal readings in cases with active hyperthyroidism. The average is considerably higher than that of the other groups (29 micrograms). The observation of Perkin[10] that a normal or low blood iodine in a patient with indisputable evidence of hyperthyroidism is a bad prognostic sign indicating a poor surgical risk and a strong possibility of a recurrence is borne out by several in this group. We have not used the iodine tolerance test as described by Perkin,[11] but hope to do so during the coming year. This test certainly seems destined to take a position along with blood sugar determinations in diabetes and the calcium-phosphorus ratio in parathyroid disorders.

Table 2

BLOOD IODINE VALUES AND BASAL METABOLIC RATES IN ENDEMIC GOITER, WITH NO EVIDENCE OF TOXICITY

Case	Diagnosis	Basal Metabolic Rate. Per Cent	Blood Iodine Micrograms
35081	Diffuse non-toxic	— 7	13.9
34054	Nodular non-toxic	+ 14	17.7
36018	Megalo-thyroid (huge cyst)	— 8	11.2
34033	Nodular non-toxic	+ 5	13.8
36029	Diffuse non-toxic	+ 25	18.4
36027	Adolescent hypertrophy	+ 2	22.8
36033	Diffuse non-toxic	+ 20	25.4
36026	Nodular non-toxic (solitary)	+ 14	26.9
36011	Nodular non-toxic	+ 2	17.8
35140	Struma lymphomatosa	— 7	9.6
31145	Diffuse non-toxic	+ 8	11.4
35164	Riedel's struma	— 22	10.1
36546	Diffuse non-toxic	— 2	9.2
36007	Adolescent hypertrophy	+ 10	15.1
34126	Nodular non-toxic	— 8	7.3
		Average	15.3

Table 3

BLOOD IODINE VALUES AND BASAL METABOLIC RATES IN CASES OF ACTIVE HYPERTHYROIDISM

Case		Basal Metabolic Rate. Per Cent	Blood Iodine Micrograms
35070		+ 35	21.38
35140		+ 32	26.9
36108	(Recurrent)	+ 56	20.11
35070	Child age 12	+ 46	20.75
35171	Boy age 17	+ 22	86.6
36002		+ 10	28.6
35122	Apathetic	+ 42	12.5
35289		+ 38	23.47
36009		+ 58	17.4
36003		+ 30	50.9
32987		+ 56	39.3
36014	Malignant exophthalmos	+ 36	43.5
36013		+ 28	20.6
34527		+ 46	38.1
36024		+ 53, + 26	27.3
36034		+ 42	22.0
36023		+ 30	21.7
			Average 29

Along with the iodine determinations we have done comparative studies on cholesterol, but our figures are not remarkable, following those of other workers rather closely. In hyperthyroidism the figures were quite low, and in hypothyroidism they were high, as was reported by Hurxthal.[12] We feel that this test is of more value in the differential diagnosis of hypothyroidism than for the cases with suspected toxicity.

At the present time we are using a rather simple test in the clinic described by Bram[13] for use in suspected cases of hyperthyroidism. He noted that patients with true hyperthyroidism has an increased tolerance for quinine, so gives the patient a stated amount of quinine sulphate or hydrobromide and observes their reaction. If they do not develop symptoms of cinchonism within four days the test is positive for hyperthyroidism. Such a test is certainly quite easy to perform, and is not beset by any dangers or particular discomforts. Our experience would indicate that it is fairly reliable, but we have not had sufficient time to make certain of these impressions. We also use another very simple procedure that has proven of value to us in the differentiation of true from suspected hyperthyroidism; that is, the response of a patient to iodine therapy. If a patient complaining of nervousness does not improve after seven to ten days of Lugol's solution in small doses, then the presumption is that the patient does not have hyperthyroidism unless there are other reasons for this response. Of course I readily appreciate the many objections to such a test, and the many fallacies that surround it, but for a simple indicator it probably has some value.

The impedance angle test as described by Brazier,[14] and based upon the known increased permeability of the tissue of a patient with hyperthyroidism to a direct electric current, has not proven accurate enough to be of dependable help (Lahey).[15] Also the mathematical computation test as described by Read, Gale and others was recently reviewed by Frank[16] and found to have a large margin of inaccuracy. In 250 patients only 20 per cent had an error of less than 5 per cent.

NEWER METHODS OF TREATMENT

In the medical management of thyroid conditions some experimental changes have been made in our methods of administering iodine. The only one of these that we have found to be of value has been the reduction of the dosage. Thompson[17] and others have shown that the maximum beneficial effect of iodine can be obtained with less than one drop of Lugol's solution per day. We have not reduced the dosage to this low figure yet, but use three minimums given twice a day, or three times a day, or more often if the case is extremely toxic. We have found this amount to be sufficient and just as effective as the larger doses. Recently Banford Jones[18] advocated the administration of iodine by intravenous injection in order to shorten the period of iodinization. This is more difficult for patient and physician and is of questionable value. Our experience in a very few cases was somewhat unsatisfactory because of severe iodine rash which may easily develop. Also the form of iodine has been varied by some physicians for uncertain reasons, as Lugol's solution is not particularly unpleasant and quite the least expensive. Di-iodo-tyrosine has been given in cases in which it is necessary to continue the administration of iodine for a long period of time, and has been found to be as effective as Lugol's solution. Boothby[19] summarizes the situation by saying:

> "Until further and conclusive evidence is advocated of the supposed specific anti-thyroxine action of di-iodotyrosine, as well as its possible calorigenic action, there is, to say the least, no point in using it in preference to the more common and much cheaper preparations of iodine. It cannot be used as a substitute for desiccated thyroid or thyroxine in the treatment of myxedema."

The use of irradiation continues to be a subject for controversy in many parts of the country. We have tried to view the situation impartially and admit to certain convictions concerning its proper place in our therapeutic equipment. According to Bauer,[20] in mild cases the best results can be obtained with irradiation therapy. Means[21] has reviewed a group of cases treated by irradiation in the "pre-iodine days," and finds that, for the most part, the cures have proven permanent. He believes irradiation to be of value in approximately one-third of the cases and helpful in an additional third. In the selection of cases for irradiation, we believe the extremely toxic patient can frequently be better prepared by use of the correct R-unit dosage of x-ray. The pregnant woman past the fourth month of

her gestation who develops symptoms of hyperthyroidism may be "tided over" until a less dangerous time for operation. Also the very aged person in poor general condition may have the symptoms so reduced in severity that he may be comfortable for many months or even years. If the physical condition improves then operation can be done with less danger.

In the preparation of the very toxic nodular goiter patient with cardiac involvement, one occasionally encounters a persistent tachycardia which does not disappear after the usual period of iodine and digitalis. For this infrequent situation we have used to advantage another one of the cardiac glucosides, thevetin. Noble and Chen[22] reported beneficial results in 18 of 22 cases of this type in which they used this drug.

In patients who show evidence of liver damage, a liver function test should be done to determine the amount of damage. Practically all cases of this type are presumed to have some degree of interference with function and an attempt is made to restore the glycogen reserve to the maximum. This means glucose daily for several days before operation, and by continuous intravenous injection for 24 to 48 hours after operation if it is considered necessary. By this procedure we feel that we have considerably reduced our operative shock, thus lowering the mortality and shortening the hospitalization period. From the standpoint of surgery the most important development in our methods of handling patients with hyperthyroidism has been a return to our previous practice of multiple stage operations in very toxic cases. Prior to 1922 polar ligations were done in these cases, sometimes in as many as four stages, taking each vessel separately, and at times having the wound opened as a preliminary stage. At one time at the Mayo Clinic[23] (1912-1916) 61 per cent of the patients had multiple stage operations performed, but following iodine preparation this figure dropped to 1.8 per cent in 1929-1934. Just now the trend seems in the other direction, for Lahey[24] states that 22 per cent of all cases operated upon for hyperthyroidism in his clinic have multiple stage procedures. The reason for this return was the occasional operative death that we found could be prevented by doing less at one sitting. The patient with extreme hyperthyroidism at any age, and the elderly individuals with cardiac involvement, particularly of the apathetic type, are the types usually selected for stage procedures. The type of operation has changed largely from polar ligations to unilateral lobectomy (hemithyroidectomy) which can be performed in a relatively short period of time without serious shock. Following the proper administration of iodine the patient usually shows a drop in pulse rate, lowering of the basal rate, and gain in weight which are approximately the same results as would be obtained by polar ligation.

In a series of 542 cases reported recently (Davison and Poer[25]), a total of 576 operations were performed, or 34 in multiple stages. Four of these patients were in the non-toxic group on account of age and poor physical condition. Twenty-eight patients with hyperthyroidism of primary or secondary type had stage operations on account of severity of cardiac complications. One young girl of twelve had such a severe exophthalmic goiter that stage operations were decided upon; at the last operation about one-third of the gland was left on account of her age, and she promptly developed a recurrence. This has been mild in comparison to her former state and has been kept under control by medical measures and irradiation. On the other hand, if too much gland tissue had been moved myxedema would certainly have followed, as did happen in one of our earlier cases. Another interesting complication followed the first stage operation in a patient with apathetic hyperthyroidism and severe decompensation (auricular fibrillation); on the fourth postoperative day she developed a psychosis from which she did not recover even though she was taken from the hospital. These are our only two bad results in this series of 34 cases, but we feel quite sure that both would not have survived a one-stage subtotal thyroidectomy.

In the Thyroid Clinic we have observed a group of patients with questionable enlargements of the thyroid, but with definite symptoms of constriction in the neck. Lateral x-rays show narrowing and deformity of the trachea, and the patient complains of difficulty in breathing, choking and occasionally of difficulty in swallowing. Many of these patients were thought to be neurotic and were referred to the Neuro-Psychiatry Department for treatment, but after failure to receive benefit they returned to us, and in desperation we attempted to do something for them.

Upon some seventeen of these cases we have done a minimal hemi-thyroidectomy (bilateral) and also removed the isthmus; no attempt is made to suture the cut surface of the gland to the sterno-hyoid muscle, as was advocated by Lahey[26] because of the feeling that the patient might continue to complain due to the adhesions created. Also an occasional scar became adherent to the underlying muscles, causing an ugly "riding" up and down with deglutition.

Total ablation of the normal thyroid gland for certain cardiac conditions is not a new procedure, but one about which there is still some argument as to indications and value. It would seem that we have passed through the period of enthusiasm during which many cases were selected for this radical procedure without sufficient cause, and consequently there were some failures and disappointments. However, at the present time it seems a well established fact that the operation is justified in those patients with progressive and recurring decompensation upon whom all known medical measures have been used with diminishing effect until finally nothing is left but continuous bed-rest, a complete cardiac invalid. The use of the operation for relief of angina should properly be left to the decision of the patient if of sufficient intelligence because of the known discomfort that accompanies a myxedemic existence. We have performed this operation upon four patients, two of each type. A patient just out of bed after relief of symptoms of decompensation returned to rather strenuous work, walking several miles each day, and promptly died from overtaxing a damaged heart. The results in the others have been quite gratifying, and all were operated upon more than a year ago.

SUMMARY

(1) The dangers of placing complete reliance upon the basal metabolic test to estimating the activity of the thyroid has been stressed.

(2) The value of the blood iodine test has been discussed and our experience with this procedure added to that of others.

(3) The relative merits of various forms of iodine have been presented. The value of diiodo-tyrosine seems questionable in the eyes of many observers.

(4) The value of irradiation as a form of treatment has been discussed and the indications for such therapy have been given.

(5) The increasing use of multiple stage operations indicates the value of this method in handling many very toxic thyroid patients.

(6) An operative method for the relief of troublesome symptoms due to constriction of the trachea has been described.

(7) Other developments in the treatment and diagnosis of thyroid conditions have been presented and discussed.

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THE USE OF PARA AMINO BENZENE SULPHONAMIDE (SULPHANILAMIDE) OR ITS DERIVATIVES IN THE TREATMENT OF INFECTIONS DUE TO BETA HEMOLYTIC STREPTOCOCCI, PNEUMOCOCCI AND MENINGOCOCCI*

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and
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Experimental and clinical observations which attest the effectiveness of para amino benzene sulphonamide or its derivatives in the treatment of *beta* hemolytic streptococcal infections are rapidly accumulating abroad and in this country. These reports[4 5 6 11] lead one to believe that these chemicals are active chemotherapeutic agents in the treatment of hemolytic streptococcal infections. In so far, however, as pneumococcal and meningococcal infections are concerned, only a few reports are extant regarding the experimental use of these chemicals as therapeutic agents. In this communication we shall discuss the experimental background and the clinical use of para amino benzene sulphonamide and its derivatives.

CHEMICAL STRUCTURE

The original "prontosil" is an azo dye, the hydrochloride of 4-sulphamido-2, 4 diaminoazo benzol. It is a red crystalline powder, soluble up to about 0.25 per cent in water and having a melting point of 247 to 251° C.[1] This preparation is not available in the United States. "Prontosil solution" is a 2.5 per cent watery solution of disodium 4-sulphamido-phenyl-2-azo-7-acetylamino-1-hydroxynaphthalene 3, 6-disulphonate. It is a reddish crystalline material and is soluble up to about 4 per cent in water.[1] Para amino benzene sulphonamide (sulphanilamide) is a white crystalline powder with a melting point of 165° C. and soluble in water at room temperature up to about 1 per cent.[2] Benzyl amino benzene sulphonamide, also a white crystalline powder, has little solubility in water.[3] The formulae for these compounds are given in Chart 1.

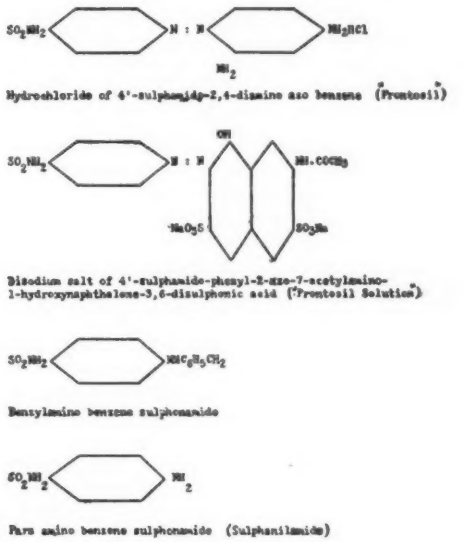
Hydrochloride of 4'-sulphamido-2,4-diamino azo benzene ("Prontosil")
Disodium salt of 4'-sulphamido-phenyl-2-azo-7-acetylamino-1-hydroxynaphthalene-3,6-disulphonic acid ("Prontosil Solution")
Benzylamino benzene sulphonamide
Para amino benzene sulphonamide (Sulphanilamide)

Chart 1
Structural formulae.

MODE OF ACTION

The mode of action of "prontosil" and "prontosil solution" upon the streptococcus was not well understood by the original German observers. Domagk[4] noted that in experimental streptococcal infections in mice, phagocytosis played an important role in clearing the treated animals of the streptococcus. He also noted that these compounds had no effect upon streptococci *in vitro*. Colebrook and Kenny[5] observed that the serum of normal human beings and that of certain laboratory animals which had been subjected to the parenteral injection of these compounds did not possess an inhibitory effect upon streptococci *in vitro*. However, the serum from patients ill with streptococcal infection did possess definite bacteriostatic effect *in vitro* after the patients had been treated with "prontosil" or "prontosil solution." We[6] were unable to confirm these observations with reference to the serum of human patients ill with streptococcal infections, but we attributed our results to the bactericidal property of the sera themselves, a

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phenomenon recently described by Tillett.[7] We[6] further noted, as did Colebrook[8] *et al*, that strong reducing agents such as formaldehyde sulphoxalate,[6] cysteine hydrochloride[9] or magnesium powder[8] would bring about a reduction of the inactive "prontosil solution" to an active form in so far as bacteriostasis was concerned. We have also observed[10] that large numbers of hemolytic streptococci have the power of partially reducing "prontosil solution" *in vitro*.

These observations point to the hypothesis[6] that in the human patient ill with a streptococcal infection a reduction of the "prontosil" to an active form is brought about through the agency of an unknown reducing system. However, as this hypothesis is based mainly upon *in vitro* experiments, we feel that one must keep an open mind, for it is possible that these chemicals may in themselves have therapeutic effects *in vivo* which are not dependent upon a reduction to an active (*in vitro*) form.

Shortly after Domagk's original report, the French observers Trefouel, Nitti and Bovet[11] reported that para amino benzene sulphonamide constituted the active fraction of both "prontosil" and "prontosil solution." These observers studied its effects in experimental infections in mice, and their observations regarding its therapeutic efficiency were quickly confirmed.[5 6 12] The bacteriostatic effect of this chemical upon *beta* hemolytic streptococci *in vitro* was noted independently by ourselves[6] and by Colebrook[8] *et al*. We also noted that the chemical exerted a definite bacteriostatic effect upon certain strains of alpha hemolytic streptococci, pneumococcus Types I and II, and certain Neisseriae, but that it had no effect upon *Staphylococcus aureus, E. coli, E. typhi* and certain other gram-negative organisms. Rosenthal[13] has reported that sulphanilamide possesses a definite bacteriostatic and bactericidal action against pneumococci *in vitro* and quotes Branham as having noted the same effects upon the meningococcus. He did not find a similar activity of the chemical against hemolytic streptococci and certain other organisms. The discrepancy between our observations and those of Rosenthal, as regards the streptococcus, can be explained upon the basis that sulphanilamide has a definite bacteriostatic action when small numbers of organisms are tested *in vitro*, but no appreciable effect when large numbers are used. Colebrook[8] *et al*. recently have reported that in addition to the bacteriostatic effect upon streptococci, sulphanilamide exerts a bactericidal effect upon these organisms *in vitro*. Our results differ from those of Colebrook *et al*. in that we[14] have been unable to note any bactericidal effect when sulphanilamide is added to broth cultures containing small numbers of hemolytic streptococci. Then, too, in our experience, when the bactericidal effect of the sera of patients undergoing sulphanilamide therapy is tested upon hemolytic streptococci *in vitro*, the results are contradictory probably because of the interfering effect of the bactericidal property of sera described by Tillett.[7] Recently we[15] have observed that hemolytic streptococci belonging to Group D (Lancefield) and certain hemolytic streptococci belonging to Group G (Lancefield) are not susceptible to the bacteriostatic effects of sulphanilamide *in vitro*. In patients suffering from a Group D hemolytic streptococcal infestation of the urinary tract, the chemical had no therapeutic effect.

From the observations just recorded, it seems quite clear that sulphanilamide has a definite bacteriostatic effect and questionably a bactericidal effect when tested *in vitro* against hemolytic streptococci, pneumococci and meningococci. However clear this mechanism is *in vitro*, studies designed to show that this effect occurs *in vivo* have been unsuccessful.

As has been pointed out, Domagk showed that "prontosil" therapy brought about a phagocytosis of the hemolytic streptococci in infected mice. This observation has been confirmed by Levaditi and Vaisman,[16] who concluded that phagocytosis occurred because the chemical either altered or destroyed the capsules of the streptococci. Neither Colebrook and Kenny[5] nor ourselves[6] could confirm Levaditi and Vaisman's observation in regard to capsular changes.

We[6 17] have studied the effects of sulphanilamide and "prontosil solution" therapy upon the exudates obtained from the peritoneums of mice suffering from experimental hemolytic streptococcal peritonitis. We observed, from hourly studies made of peritoneal exudates, that even when sulphanilamide was injected directly into the peritoneal cavity, no evidence of either bacteriostatic or bactericidal effect *in vivo* could be obtained. If immediately before starting treatment the exudate showed 10 to 15 pairs or chains of organisms per oil immersion field, then for several hours after therapy, the organisms multiplied as though unhampered by the sulphanilamide. This multiplication continued until

suddenly a wave of phagocytosis, in which the polymorphonuclear leukocytes played a leading role, occurred. The time of this phenomenon varied in different mice and occurred from 6 to 15 hours after treatment had been started. When once established, the phagocytosis of the organisms proceeded at a rapid rate, provided that therapy was continued, until the peritoneal cavity was cleared of streptococci. It was obvious that something had happened to the streptococci which rendered them susceptible to phagocytosis, because in the control mice, multiplication continued and the animal was soon overwhelmed by the infection. We know that dead streptococci or streptococci opsonized by specific immune serum are susceptible to phagocytosis. Studies which we undertook, to determine whether the chemical killed or injured the organisms *in vivo*, have so far been unsuccessful. Organisms from the exudate of the treated animals always produced "mucoid" or "matt" colonies upon suitable media, the exudate remained highly virulent when injected into normal mice, even when subcultures proved sterile, providing that phagocytized organisms could be seen in properly stained specimens and as long as free organisms remained in the exudate, their capsules seemed to be unimpaired.

Thus, from *in vivo* experiments, we can only conclude that a change takes place in the streptococci which renders them susceptible to phagocytosis, but the nature of this change is still unknown. Certainly we have no evidence that the bacteriostasis observed *in vitro* plays an important role *in vivo*. It is important to note, however, that the change brought about by sulphanilamide therapy is not instantaneous, but requires a period of several hours before it begins to develop. This suggests the possibility of a union between the organism and chemical by which a marked change in the metabolism of the streptococcus is brought about. We believe that sulphanilamide exerts its action upon the streptococci rather than upon the leukocytes, because it has long been established by Bordet[18] that the leukocytes from the exudate in experimental streptococcal peritonitis due to highly virulent organisms are capable of phagocytosis of other organisms, but not of the streptococci.

THE EFFECT OF SULPHANILAMIDE OR ITS DERIVATIVES UPON EXPERIMENTAL INFECTIONS IN ANIMALS

The chemotherapeutic effects of sulphanilamide or its derivatives upon experimental hemolytic streptococcal and meningococcal infections in animals have been amply demonstrated.[4 5 6 11 19] However, in discussing the striking effects obtained in the treatment of experimental infections, we should like to detail the subsequent histories of the two groups of 24 mice infected with the hemolytic streptococcal strains C203 and Schw which we have previously described.[6] All of the 24 mice infected with strain Schw have succumbed; 15 died of hemolytic streptococcal infection, while 9 succumbed to intercurrent mouse infection. The last survivor in this group, dying of streptococcal infection, lived 63 days after infection and 49 days after treatment was discontinued. One mouse of the C203 group still survives. Twelve have died of hemolytic streptococcal infection, the last one 128 days after infection and 114 days after treatment had been stopped. These late deaths from hemolytic streptococcal infection add weight to our belief that sulphanilamide or its derivatives have no direct bactericidal effect upon streptococci *in vivo*.

In their original report Buttle[12] and his coworkers stated that sulphanilamide had no curative effect in experimental Types I and II pneumococcal infection in mice. Recently Rosenthal[20] has reported that the chemical exerts some curative effects in Types I, II and III experimental pneumococcal infection in mice. He reported survivals for at least seven days in 25 per cent of the mice infected with Types I and II pneumococci. In mice infected with Type III pneumococci 42 per cent survived. At about the same time that Rosenthal's investigations were in progress, we were testing the curative effects of sulphanilamide in experimental pneumococcal infection in mice. The results of our observations are outlined in *Table 1*.

As has been shown in *Table 1*, all of the mice inoculated with Types I, II or III pneumococci have succumbed to their infection regardless of whether or not they were treated with sulphanilamide. In this respect our experience differs somewhat from that of Rosenthal,[20] who reported more survivals. It was interesting to note in the treated mice that many appeared to be well and healthy at the time of the death of the control mice. Then, at varying periods, the treated mice would become ill and die of pneumococcal infection despite adequate therapy with sulphanilamide. Thus the chemical apparently has the power of holding the infection in check for a while, but eventually the chemotherapeutic

THE EFFECT OF PARA AMINO BENZENE SULPHONAMIDE THERAPY IN EXPERIMENTAL PNEUMOCOCCAL INFECTION IN MICE

Date	Type	No. of Mice	Infecting Dose	M.L.D.	Time of Treatment	Total Therapy	Survival Period, Hours	Average Survival Period, Hours
10/26/36	II	3	10-7	10-9	10 min.	48 mg.	23, 45, 54	41 hours
10/26/36	II	2	10-7	10-9	Control		19, 20	19.5 hours
10/29/36	II	9	10-6	10-9	10 min.	88 mg.	360, 59, 48, 72, 72, 72, 59, 96, 59	99 hours
10/29/36	II	6	10-6	10-9	4 hours	72 mg.	75. 48, 48, 52, 59, 72	26 hours
11/27/36	I	4	10-4	10-6	5 hours	76 mg.	121, 72, 72, 57	53 hours
11/27/36	I	4	10-4	10-6	Control		23, 25, 26, 48	30 hours
11/30/36	I	8	10-4	10-6	2 hours	68 mg.	128, 168, 144, 73, 77, 72, 74, 30	108 hours
11/30/36	I	12	10-4	10-6	Control		26, 26, 48, 48, 48, 48, 48 48, 48, 48, 31, 32	41 hours
2/ 4/37	III	8	10-5	10-7	2 hours	32 mg.	44, 44, 44, 44, 68, 68, 68, 52	54 hours
2/ 4/37	III	8	10-5	10-7	Control		26, 29, 36, 36, 23, 23, 48, 48	33 hours
2/ 8/37	III	6	10-6	10-8	15 min.	56 mg.	118, 94, 70, 94, 142, 94	105 hours
2/ 8/37	III	3	10-6	10-8	Control		22, 25, 28	35 hours

effect is lost and the mouse succumbs to pneumococcal infection.

THE PHARMACOLOGICAL EFFECTS OF SULPHANILAMIDE AND ITS DERIVATIVES

Very little has been done on the pharmacological effects of "prontosil" or "prontosil solution." Horlein[1] reported concerning "prontosil":

"Intravenously, mice tolerate 1 c. c. of the 0.25 per cent solution per 20 gram body weight, and rabbits up to at least 10 c. c. of the 0.25 per cent solution. The substance could be given to rabbits by mouth for long periods, e. g., 0.1 to 0.2 gram kg. body weight for 14 days, without harming the general condition of the animal, and without causing any alteration in the composition of the blood, or pathological change in the urine. When given in large quantities the dye penetrates into all the tissues, which probably explains its potent action on streptococci localized in the most varied situations in the body. So far we have not been able to demonstrate microscopically any accumulation of the dye in particular organs or cells. The dye is, in part, rapidly excreted in the urine, giving the latter a yellowish-red color half an hour after its administration by mouth, but no albuminous casts or white blood corpuscles were ever seen after the administration of "prontosil." The weight of the animals remained unchanged. According to the work of Weese and Hecht, "prontosil" is pharmacologically an extraordinarily negative compound. No change in the blood pressure or heart function could be demonstrated after the rapid intravenous injection of 10 mg./kg. body weight. Also, the smooth muscle of the uterus, and of the large and small intestine, whether investigated in the isolated state or *in situ*, did not respond to "prontosil." The physiological functions of these organs were unaffected by "prontosil." No harm was ever observed when doses of 1 gram/kg. were injected subcutaneously into animals."

Allport[21] has suggested the following standards for para amino benzene sulphonamide:

"Melting point, 165 to 166.5° C. Reaction of a 0.5 per cent aqueous solution, pH 5.8 to 6.1. Ash, not more than 0.02 per cent. Arsenic, not more than 1 part per million. Heavy metals, calculated as lead, not more than 5 parts per million. Chlorides and sulphates should not be present in more than the faintest traces. When assayed on its sulphur content by the method described, not less than 99.5 and not more than 100.5 per cent of *p*-aminobenzenesulphonamide should be indicated."

It is difficult to attempt a rational method of therapy with a given drug unless something is known about its absorption and excretion. Fuller[22] has recently discussed this problem. He found that in normal animals 65 per cent of injected sulphanilamide and 51 per cent of "prontosil solution" could be accounted for by its excretion in the urine. In infected animals these

discrepancies were greater. The infected animals receiving "prontosil" excreted more sulphanilamide than did the normal animals. He was unable to arrive at any definite knowledge of the relative therapeutic values of the "prontosils" and sulphanilamide by determining the modes of absorption and of excretion of these products. In summarizing his conclusions he states that a considerable amount of sulphanilamide is excreted when "prontosils" are given, and that the therapeutic action of these chemicals may be due to sulphanilamide derived from them by reduction in the body.

Recently Marshall, Emerson and Cutting[24] have reported a method for determining the sulphanilamide content of body fluids. These observers noted after a single peroral dose in dogs that the chemical was practically completely absorbed within three to five hours, and that it was largely excreted in the urine within 48 hours. The subcutaneous administration of the drug in dogs did not result in a more rapid absorption into the blood stream. In rabbits, the compound was partially excreted in a conjugated form which they identified as being para acetyl aminobenzene sulphonamide.[24]

In man the drug was excreted partly unchanged and partly in the conjugated form. After a single dose of the chemical by mouth in man, absorption appears to occur within 3 to 4 hours, as at this time a peak was reached in the blood sulphanilamide level. Then the blood level fell steadily and at the end of 24 hours, a major part of the compound was found to have been excreted. Marshall and his associates noted in a patient with serious renal impairment that the excretion of the compound was markedly retarded and that the blood level rose rapidly. It was also noted that the drug passed readily into the spinal fluid and into empyema, ascitic and other body fluids. In these fluids it was present in slightly lower concentration than in the blood.

The observations of Marshall and his associates have been of prime importance in establishing a rational basis for therapy in infected human beings. With an accurate and adequate method for determining blood sulphanilamide levels, it is now possible to determine quickly whether or not absorption occurs after oral administration, and to correlate clinical improvement in patients with blood sulphanilamide levels.

THE CLINICAL USE OF SULPHANILAMIDE OR ITS DERIVATIVES

Beta Hemolytic Streptococcal Infections.—We have found that sulphanilamide and "prontosil solution" are effective chemotherapeutic agents in infection caused by Groups A and B *beta* hemolytic streptococci, but that they were valueless in 4 patients with infections caused by Group D hemolytic streptococci.

During recent months our therapeutic experience with these chemicals has increased. In addition to the patients treated at the Johns Hopkins Hospital, we have been able through the courtesy of Dr. Walter Baetjer and the staff of the Union Memorial Hospital, and of Dr. Francis Schwentker of Sydenham Hospital, to observe patients treated with sulphanilamide or its derivatives. As a result of these clinical studies, it would seem that sulphanilamide *per os* is the drug of choice. If, however, the patient cannot swallow tablets, or oral administration of sulphanilamide is not desirable, we use either "prontosil solution" or an 0.8 to 1 per cent solution of sulphanilamide in sterile physiological saline solution. These solutions are given parenterally by the subcutaneous route.

In our previous communication[6] we came to the conclusion that a 1-10,000 concentration of sulphanilamide was definitely bacteriostatic *in vitro*, that this would constitute an effective therapeutic level *in vivo*. Our earlier system of dosage was therefore based upon amounts of sulphanilamide which would theoretically give us this concentration.

However, with the advent of Marshall's method for determining blood sulphanilamide levels accurately, we have been able, in conjunction with Dr. E. K. Marshall, Jr., and his associates, to determine the amount of the drug best suited for clinical therapeutics.

As has been pointed out, Marshall and his associates noted that in the human being absorption from a single dose of the chemical given by mouth was essentially complete within 4 hours. The observation is of value in establishing the spacing of doses of the drug when the maintenance of a proper blood level is desired. Since, in patients with severe hemolytic streptococcal infection such as meningitis, septicemia and peritonitis, it is desirable to reach a high blood level of the chemical rapidly, we feel that in such instances it is rational to administer a large initial dose of sulphanilamide with the

aim of attaining a blood level of 10 mg. per cent within 4 hours.

Hence, in adult patients, that is, those weighing 100 pounds or more, who are suffering from severe streptococcal infections, we administer an initial dose of from 10 to 16 five-grain tablets. This initial dose should give a blood level of about 10 mg. per cent within 4 hours. Then, to maintain this level, we advise 3 five-grain tablets every 4 hours. If the patient weighs 50 to 90 pounds, the initial dose should be 6 to 10 five-grain tablets followed by 2 or 3 tablets at 4-hour intervals. In children weighing from 25 to 50 pounds, 4 to 6 five-grain tablets constitute the initial dose followed every 4 hours by doses of 1 or 2 five-grain tablets. Patients excrete the drug at slightly different rates, so the maintenance dose may vary somewhat.

We have found it advantageous to determine the blood sulphanilamide level 4 hours after the initial dose. If the blood does not show the expected level of 8 to 10 mg. per cent, then parenteral administration of the chemical should be instituted. It is of value to check the blood sulphanilamide level 24 hours after therapy has been started to determine the adequacy of the maintenance dose of the drug.

The preparation of sulphanilamide for parenteral use is simple. This chemical is soluble up to 1 per cent in physiological saline solution at 37° C. It is our practice to bring the required amount of sterile physiological saline solution to a boil. It is then removed from the flame, and as soon as it stops boiling, 0.8 to 1 gram of sulphanilamide is added per 100 c. c. of physiological saline solution. The hot saline solution is then agitated to facilitate the dissolution of the sulphanilamide, cooled to 37° C., and is administered by hypodermoclysis. A 1 per cent solution will remain fairly stable if kept at room temperature. If the temperature falls, or if the solution is placed in an ice box, the sulphanilamide crystallizes out of solution rapidly. It is our custom to make up the daily requirement of sulphanilamide solution for a patient each morning.

Our experience in the use of parenteral sulphanilamide solution leads us to believe that the following amounts represent adequate therapeutic doses. In adults, the initial hypodermoclysis should be 700 c. c. of an 0.8 to 1 per cent solution, followed by 500 c. c. at 8-hour periods during the first 24 hours. The initial dose for individuals weighing from 50 to 90 pounds should be from 300 to 500 c. c., followed by 200 to 300 c. c. at 8-hour intervals. Children weighing 25 to 50 pounds should receive an initial dose of 100 to 300 c. c. of sulphanilamide solution, this to be followed with 100 to 200 c. c. of the solution at 8-hour intervals. In babies it is difficult to determine the dose, but they should receive about 1 gram of sulphanilamide per 10 pounds of body weight during the first 24 hours.

Sulphanilamide solutions may be given by the intrathecal route in the treatment of streptococcal infections of meninges. The drug has not been found irritating to the meninges and the technic of administration is the same as that used in giving antisera by this route. The solution is warmed to 37° C. and after the spinal drainage has been completed, an amount of sulphanilamide solution equivalent to 5 or 10 c. c. less than the amount of cerebrospinal fluid which has been removed is permitted to run into the spinal canal under the force of gravity. Never inject the solution under positive pressure. Intrathecal therapy may be given at 8-hour periods in infections of the meninges.

"Prontosil solution" should be given by the subcutaneous route. It is absorbed rapidly and is practically non-irritating. For 2 or 3 minutes after its injection, a sensation of burning or stinging may be noted at the site of injection. This may be obviated by infiltrating the area of injection with a small amount of a local anesthetic. The drug is absorbed rapidly, and has been noted in the urine within 15 minutes after a single subcutaneous injection of 100 c. c. of the solution. Because of the frequency with which the drug is given, we start its administration in the right pectoral region and proceed to the left pectoral region, then to the outside, top and inside of both thighs, and next to each of the buttocks. Following the injection in the buttocks, one may return to the right pectoral region.

In adults the therapeutic dose of "prontosil solution" is 20 c. c. at 4-hour intervals, or a total of 120 c. c. of the solution in 24 hours. Individuals weighing 50 to 90 pounds should receive from 10 to 15 c. c. of the drug at 4-hour intervals. Children weighing from 10 to 50 pounds should receive 5 to 10 c. c. every 4 hours. These doses should be continued in each instance until a definite clinical effect has been obtained. Then the dose may be gradually decreased. It

will be noted that doses of "prontosil solution" such as we have recommended will color the skin pink and the urine a bright red. "Prontosil solution" is definitely irritating when given intrathecally, and should not be administered by this route. Severe reactions may occur after the intravenous administration of the drug.

So far we have discussed only the maximum dosage which is used in very severe streptococcal infections. In moderately severe infections, we have noted that 2 or 3 five-grain tablets of sulphanilamide, administered at 4-hour intervals, constitutes an effective dose in adults, while 1 or 2 tablets at 4-hour intervals can be given to children. For very mild infections, the dose of the chemical may be decreased to 1 tablet 3 or 4 times a day.

After definitely favorable clinical effects in the patient have been obtained, the dose of sulphanilamide should be rapidly decreased. At first, the dose may be cut by one-third. Then if the improvement in the patient's condition is continued, the drug should be cut to one-third of the original amount. This should be continued until convalescence is well established. We have found that lesions of the bones, such as otitis media, mastoiditis and osteomyelitis require long-continued treatment, and in patients suffering from these lesions we continue therapy (in small amounts) for at least 2 weeks after a clinical cure has been effected.

Sulphanilamide may be used as a prophylactic against hemolytic streptococcal infections in times of epidemic outbreaks of this type of infection. In adults 2 five-grain tablets at 4-hour intervals for 4 doses a day constitute the prophylactic dose. Children should receive 1 five-grain tablet 4 times a day.

It has not been possible to obtain adequate controls for the various types of *beta* hemolytic infections in human beings which have been treated with sulphanilamide or its derivatives. Hence, the striking results obtained in many hemolytic streptococcal infections might be due to chance. It is well known, however, that hemolytic streptococcal meningitis has a case fatality rate of 98 per cent. During the past 4 months we have known of 10 patients ill with this disease. All were treated with sulphanilamide or its derivatives, and 8 of the 10 patients recovered from their disease.

Pneumococcal Infections.—Our experience in the treatment of clinical pneumococcal infections in human beings has been primarily limited to those of the middle ear and mastoid. In the treatment of pneumococcal otits media and mastoiditis we have used sulphanilamide alone as the therapeutic agent. The dosage has been comparable to that used in streptococcal infection. Our observations tend to show that sulphanilamide has about one-half the chemotherapeutic effect in pneumococcal infections that it has in hemolytic streptococcal infections of the middle ear and mastoid. These clinical observations bear out our experimental findings in regard to the therapeutic effects of sulphanilamide in experimental pneumococcal infections in mice.

Meningococcal Infections.—Schwentker and his associates[25] have recently reported that sulphanilamide exerts a curative effect comparable to that obtained with good anti-meningococcal sera in meningococcal meningitis and septicemia in human beings. These patients were treated both by the subcutaneous and intrathecal routes. The evaluation of sulphanilamide therapy alone in meningococcal infections necessarily awaits more extensive studies, but in view of the experimental observation upon this subject and the reported favorable results in human infections, it seems reasonable at the present time to use sulphanilamide as an adjunct to serum therapy in meningococcal infections.

THE TOXIC EFFECTS OF SULPHANILAMIDE OR ITS DERIVATIVES

It is of utmost importance in the study of any new therapeutic agent to determine as early as possible its toxic effects. Colebrook and Kenny[5] reported that the "prontosils" had a mildly irritative effect upon the kidney, and that these compounds produced sulphemoglobinemia in 3 of their patients. They believed, however, that the association of saline cathartics with the therapeutic administration of the "prontosils" was a contributing factor in the production of the sulphemoglobinemia, and advised against the use of saline cathartics in patients receiving "prontosil."

In our experience "prontosil solution" has produced but one toxic effect, namely, fever. This manifestation appears constantly in those normal subjects who have been tested with a single

large dose (100 c. c.) given by the subcutaneous route. It also occasionally is seen on the third day or later of continuous "prontosil solution" therapy. It is our practice to discontinue "prontosil solution" if fever appears which is considerably out of proportion to the general clinical condition of the patient. As this generally occurs at a time when the streptococcal lesions is rapidly regressing, the clinical problem involved is not difficult. We have not seen any evidence of renal irritation in patients receiving "prontosil solution."

On the other hand, sulphanilamide has certain mild but definite clinical toxic effects. In normal human beings the ingestion of 10 five-grain tablets is followed in 6 hours by slight dizziness and mild nausea. Ambulatory patients who are suffering from streptococcal infections often complain of dizziness, anorexia, nausea and sometimes of a sensation which is described as being similar to that experienced when mildly intoxicated with ethyl alcohol. These effects, however, are rarely noted in patients who are kept in bed during the period of therapy.

A second, very frequent, toxic manifestation is cyanosis, which is sometimes associated with methemoglobinemia. Cyanosis has been noted in three-quarters of the patients treated with sulphanilamide, and varies in intensity from a mild bluing of the lips to a rather intense slaty discoloration of the lips and nail beds. The mechanism of the development of the cyanosis is as yet unknown. We do not regard cyanosis as an indication that therapy should be discontinued. We have seen patients in whom cyanosis made its appearance within 5 hours after sulphanilamide therapy had been started, and in whom it disappeared in a few days despite the fact that intensive sulphanilamide therapy was continued until convalescence was established. We have observed 3 patients in whom sulphemoglobinemia was detected in the blood. None of them had received saline cathartics, so it is quite possible that the chemical itself is capable of producing sulphemoglobinemia.

Practically every patient who receives sulphanilamide in therapeutic doses shows a fall in the carbon dioxide combining power of the blood. We have seen 4 cases of clinical acidosis, characterized by air hunger, and an alkaline urine without ketonuria, which have developed in the course of sulphanilamide therapy. This toxic manifestation of the drug has been studied in the medical clinic of the Johns Hopkins Hospital by Southworth,[26] who noted that a variable but consistent drop in the carbon dioxide combining power of the blood plasma occurred in 15 consecutive cases of streptococcal infection which had been treated with sulphanilamide. The exact mechanism of this phenomenon is not clear, but we are studying it at the present time. We have found that the administration of 10 grains of bicarbonate of soda with each dose of sulphanilamide is of value in preventing the fall in the carbon dioxide combining power, and at the present time we routinely administer bicarbonate of soda with each dose of sulphanilamide.

If an acidosis should develop, the administration of 1/6 molar sodium lactate solution by the intravenous and subcutaneous routes is of definite value in combating this toxic manifestation of sulphanilamide therapy. In babies, frequent small hypodermoclyses of 1/6 molar sodium lactate solution may be used to prevent acidosis.

We have previously stated that "prontosil solution" may cause fever. This is also true of sulphanilamide. When this occurs, it is best to stop the drug for 2 or 3 days, during which period the temperature will fall to normal if the fever is due to the sulphanilamide therapy.

We have carefully studied the urine of patients receiving sulphanilamide without noting signs of renal irritation. As we have stated previously, sulphanilamide is not excreted rapidly by the damaged kidney, and hence it tends to accumulate in the blood of patients having decreased renal function. We believe that if the drug is to be used in patients with decreased renal function, the sulphanilamide blood levels should be followed at daily intervals. When the blood sulphanilamide level reaches 15 to 20 mg. per cent, the drug should be stopped.

It must be always borne in mind that sulphanilamide or its derivatives contain the benzene ring, which may damage the hematopoietic system in patients who have an idiosyncrasy towards the benzene ring. We have seen two patients who have developed acute anemias of a severe degree while under treatment with sulphanilamide. We are not prepared to state whether these anemias represent the toxic effects of, or an idiosyncrasy to the drug. It is also probable that in susceptible patients a granulocytopenia will occur after the administration of the drug.

In patients suffering from the acute toxic manifestations of sulphanilamide therapy, we have found that large amounts of fluids act as

an antidote. We have seen one patient who took 12 grams of sulphanilamide within 12 hours and who developed headache, dizziness, nausea and a moderate degree of cyanosis. Inasmuch as we know that the chemical is excreted with water, we had this patient force fluids to the extent of taking 5,000 c. c. of water by mouth within a 6-hour period. The drug was rapidly excreted, and after a few hours all signs of toxicity disappeared.

SUMMARY

Para amino benzene sulphonamide (sulphanilamide) or its derivatives are potent chemotherapeutic agents in the treatment of hemolytic streptococcal infections and have some therapeutic value in pneumococcal and meningococcal infections. Comparatively little, however, is known of the toxic effects of these compounds, and, because of this, we feel that a long-continued clinical experience with these chemicals will be needed before they can be accurately evaluated as therapeutic agents.*

*The "prontosil solution" used in these studies was supplied by the Winthrop Chemical Company. Para amino benzene sulphonamide (sulphanilamide) was supplied by E. I. duPont de Nemours & Co., the Winthrop Chemical Company, Abbott Laboratories, E. R. Squibb & Sons, and Merck & Co., Inc.

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PHLEBITIS OF THE LATERAL (SIGMOID) SINUS IN INFANTS AND CHILDREN*

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The occurrence of sepsis as a result of involvement of the lateral sinus secondary to mastoiditis is always a potentially serious complication, and very often presents difficulties both in diagnosis and treatment. Opinions and recommendations offered by members of the pediatric, otolaryngological and neurosurgical staffs most responsible for the care of such cases in the wards of the St. Louis Children's Hospital during the past few years were often so divergent that, as the first step necessary for a more complete understanding of the subject, we were prompted to review our past experiences with this complication. We hoped particularly that in so doing we might be permitted better to recognize the condition early, and with some actual foundation of fact recommend a certain plan of management which has gradually become adopted as so far the most satisfactory. With but two exceptions (in which, however, the diagnosis seemed extremely probable), all the cases studied in this report were diagnosed positively either at operation or at autopsy.

In 42 cases (70 per cent) involvement of the lateral sinus apparently occurred within two months of the primary attack of otitis media. In the other 18 cases there was a history of previous otitis, often with frequent recurrences. Usually an acute upper respiratory tract infection shortly preceded sinus symptoms.

III. PATHOLOGY (AT OPERATION OR POSTMORTEM)

(A) *Mastoid.*—There was nothing characteristic, the findings varying from the acute hemorrhagic type to the sclerotic. Usually a subacute type with the antrum and cells filled with pus and granulations was encountered. Occasionally, however, much of the mastoid was either uninvolved or healed, except for cells immediately overlying the lateral sinus.

(B) *Lateral Sinus.*—Changes varied from just discoloration of the wall to complete thrombosis. In one instance there was complete obliteration, with abscess at site. Sometimes clot was firm; other times, broken down. Sometimes a *mural* thrombus was present, with the vein still patent. Occasionally the sinus looked all right when and where first exposed, showing change later.

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SUMMARY OF ANALYSES OF ALL CASES OF LATERAL SINUS PHLEBITIS ENCOUNTERED IN THE ST. LOUIS CHILDREN'S HOSPITAL FROM 1920 TO JUNE 1, 1936

I. INCIDENCE

A. By Year:

1920 = 1 (0)*	1927 = 1 (1)	1932 = 8 (6)
1923 = 1 (0)	1928 = 1 (0)	1933 = 5 (1)
1924 = 4 (1)	1929 = 6 (2)	1934 = 2 (0)
1925 = 3 (0)	1930 = 6 (2)	1935 = 6 (3)
1926 = 6 (4)	1931 = 3 (0)	1936 = 7 (1)

Total = 60

*The figures in parentheses indicate fatalities.

B. By Age:

No. fatalities	3	1	1	1	1	3	2	1	0
Age	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9
No. cases	3	2	3	2	3	7	10	7	6

30 or 50%

No. fatalities	0	3	2	2	1	0
Age	9-10	10-11	11-12	12-13	13-14	14-15
No. cases	2	4	3	3	5	0

C. By Sex:

Male = 32
Female = 28

D. By Location:

Right: Left = 3 : 2
Bilateral in 5 cases

II. ETIOLOGY

Bacterial studies in 51 cases:

Streptococcus hemolyticus

Mastoid and/or Sinus and/or Jugular vein and/or Blood } in 44 cases, or 88%

Staphylococcus ..... in 4 cases
Pneumococcus ..... in 1 case
B. mellanino genicum ..... in 1 case
Gram negative bacillus (unidentified) ..... in 1 case

(C) *Dura.*—Usually found normal, but occasionally pink, sometimes tense. In one instance without subsequent complications, it was black over an area as large as a quarter.

(D) *Jugular Vein.*—Usually looked normal. Sometimes there were associated enlarged lymph nodes (5 cases). It was found thrombosed in 5 cases.

IV. DIAGNOSIS

An absolute diagnosis of lateral sinus phlebitis cannot, of course, be made except by actual inspection of the vein. We have come to feel, however, that certain findings permit a clinical diagnosis to be made with sufficient certainty to justify operative procedures. They are the presence of (1) mastoiditis, (2) a more or less persistent septicemia, and (3) a complete or partial venous block. The data referable to these points follow:

(A) *Mastoiditis.*—Tenderness was noted in 36 cases (60 per cent), often also redness and edema, making the diagnosis simple. In the other 24 cases not showing local manifestations, x-ray was of help in 15 cases. X-ray changes were often bilateral and sometimes showed less on the side of the lateral sinus involvement. A clot in the lateral sinus was never demonstrated with certainty, but an inequality of size was sometimes noted, which had to be considered in interpreting the Queckenstedt test. X-rays in infants under one year were usually of little help, except that they occasionally revealed unexpectedly well pneumatized mastoids. In those cases showing neither local nor x-ray evidence, the diagnosis had to be made from the history of the otitis media, the appearance of the drum head and canal wall, the character of the discharge, and so on. In 2 cases the diagnosis was not made until postmortem. In several cases the otitis and mastoiditis had almost completely healed, all of which forces us to conclude that: "When the mastoid has once been involved, one cannot be sure of what might be present at the time of a later flare-up in the ear."

(B) *Septicemia.*—Suggested by the frequent occurrence of chills accompanied by an irregular septic type of fever, a so-called "septicemic blood picture," and the presence of infection elsewhere which could be of metastatic origin. Proven by positive blood cultures.

(1) Chills noted in 22 cases (more than one-third).

(2) Septic fever present in most of the cases. Not infrequently fluctuations of 10° F. were noted. Such a temperature curve is not by any means absolutely diagnostic of lateral sinus phlebitis, even if accompanied by otitis media and mastoiditis. Pneumonia especially has to be excluded; it sometimes may be embolic, making the problem still more difficult.

(3) In the hemogram, usually there is leukocytosis with left shift. In many instances leukocytosis and left shift were very slight, despite persistently positive blood cultures.

(4) Metastatic lesions were found pre- and postoperatively in 26 cases (43 per cent).

Arthritis in 12 cases (20 per cent), often multiple.

Pulmonary involvement in 10 cases (17 per cent).

Meningitis in 12 cases (20 per cent). Sometimes due to direct extension.

Soft tissue abscesses in 7 cases.

Osteomyelitis in 1 case.

(5) Blood cultures were made in 54 of the 60 cases.

Positive in 36 cases (usually repeatedly).

Negative in 15 cases (usually not repeated).

Indeterminate in 3 cases (contaminated).

In the positive group, first culture was sometimes negative.

Negative cultures should not be considered significant if obvious metastatic lesions have developed. All but 4 of the positive cultures were *Streptococcus hemolyticus.*

(6) Bacteriology in all other cases of septicemia (exclusive of *B. typhosus*) from 1916 to 1935:

	No. Cases	Per Cent	Mortality Per Cent	Chief Clinical Affection
Streptococcus	198	49	83	Upper respiratory infection
Staphylococcus	114	28	89	Osteomyelitis
Pneumococcus	38	9	97	Pneumonia
B. coli	17	4	90	Diarrhea
B. influenza	18	4	82	Meningitis
Meningococcus	8	2	38	Meningitis
Miscellaneous	14	4	71	
	405		85	—

(C) *Venous Block.*—Occasionally there was adenitis with tenderness along the course of the jugular vein.

1. Queckenstedt test:

Made in 35 of the 60 cases:
Positive in 30
Right = 13
Left = 13
Right and left = 4
Negative in 3
Questionable in 2

In 4 of the 5 cases failing to give positive tests, mural thrombi with still patent channels were found. In the remaining case a rise only from 150 mm. water pressure to 180 mm. occurred on either side, and at operation the left lateral sinus could not be identified, being replaced in the area exposed by infected granulation tissue and pus. The posterior portion of the sinus was visualized by x-ray; there was no visualization of a sinus on the right side where the mastoid looked normal. In a number of instances, however, the Queckenstedt test was negative at first, later becoming positive, presumably as the thrombosis became more complete.

2. Papilledema (with or without demonstrable increase in spinal fluid pressure):

Looked for in 34 cases
Present in 14 cases
Doubtful in 4 cases
Absent in 16 cases

All patients with papilledema had positive Queckenstedt tests, but not all patients with positive Queckenstedt tests had papilledema. All the patients, however, with bilateral positive Queckenstedt tests had papilledema (5 diopters in one instance). The spinal fluid pressure in one case was more than 750 mm. water.

V. CLINICAL COURSES OF OPERATED CASES

(A) Uncomplicated, quick, or only slightly delayed postoperative recovery, in 22 cases.
(B) Complications with early death in 12 cases.
(C) Complications with eventual recovery in 16 cases.
(D) Complications with eventual death in 7 cases.
(E) Neurological manifestations:
1. Frank disseminated meningitis in 10 cases (all fatal).
2. Pleocytosis without organism in 5 cases.
3. Brain abscess frequently suspected, but apparently did not occur in any of the 60 cases.
4. Optic atrophy in 2 cases.

VI. OPERATIVE PROCEDURES

(A) Always included thorough simple mastoidectomy.
(B) Usually included ligation of jugular vein.
(C) Usually included incision of lateral sinus until free bleeding from the posterior end was encountered.

The time of operation and sequence of steps varied.

VII. RESULTS

(A) Over Entire Period:

Recovery in 39 cases.

Death in 21 cases (35 per cent).

Twelve of the deaths resulted from meningitis (20 per cent of all the cases and 57 per cent of the fatal ones).

The remainder of the fatal cases died of sepsis resulting from pulmonary or cardiac involvement.

Three patients died unoperated upon, one being moribund on admission, the other two undiagnosed.

(B) Past 2½ years (3 Winters):

Operated cases = 14

Deaths = 3 (21.4 per cent).

One of the fatal cases had meningitis at the time of admission to the hospital.

Another had acute vegetative endocarditis engrafted on previous rheumatic valvular disease.

The other developed mediastinitis and numerous metastatic lesions, showing very little resistance anywhere to the streptococcic infection.

Improvement probably due to:

(1) Earlier recognition.
(2) Better operative methods.
(3) Better preoperative and postoperative supportive treatment (fluids, blood, lumbar puncture, etc.)

COMMENT

Incidence.—Although there was some variation in the number of cases seen per year during the period of study, the most interesting point concerns age incidence. It will be noted that, although lateral sinus phlebitis occurred in every year of life up to the fifteenth year, which marks the upper age limit as far as hospital admissions are concerned, just one-half occurred between the ages of five and nine. The explanation probably is to be found in the increased incidence of upper respiratory tract infections during this period of starting school with its exposure. No significance is to be attached to the slight predominance in the males.

As in other reports in the literature, we also noted greater frequency of involvement of the right lateral sinus, the ratio being 3 : 2. No satisfactory explanation can be thought of at the present time to account for this difference.

Etiology.—In 28, or roughly one-half, of the cases no clear statement was made descriptive of a clinical etiology. In 14 instances apparently acute upper respiratory tract infections, sometimes described as "colds," were recognized by the parents as the beginning of otitis media. In 10 instances the otitis media was a part of scarlet fever, while twice it followed closely upon surgical removal of tonsils and adenoids. It is perhaps of special importance to note that a majority of the cases (70 per cent) exhibited symptoms referable to lateral sinus phlebitis

within two months of the primary attack of otitis media, and in the remaining cases there was the history of previous otitis media, often with frequent recurrences, sometimes becoming chronic, but in such cases there was also usually a history indicative of an acute upper respiratory tract infection shortly preceding lateral sinus symptoms. The striking preponderance of the hemolytic streptococcus as the bacterial cause should be especially emphasized.

Diagnosis.—As may be noted from the previous summary, we have come to feel that the clinical diagnosis of lateral sinus phlebitis depends chiefly on the recognition of mastoiditis, proof of continued septicemia, and the demonstration of partial or complete venous block, and some further comment is in order concerning these points. It cannot be emphasized too strongly that a regularly or irregularly remittent fever in itself is not proof of septicemia.* It is, of course, common knowledge that children with pneumonia, pyelitis, sinusitis, arthritis, and other infections, may have a fever of a "septic" type with persistently negative blood cultures. Not infrequently, however, pneumonia develops following an acute upper respiratory tract infection which has led also to purulent otitis media and mastoiditis, the patient usually showing an increase of fever at the onset of the pneumonia. The physical signs of pneumonia may, however, be doubtful or entirely absent for a number of days. X-ray examination of the lungs is extremely helpful in such cases in recognizing such a pulmonary involvement, and if the latter is not accompanied by positive blood cultures, or by some other evidence of hematogenous spread of the infection, it may be safely concluded that the pneumonic process has not developed by way of an infected embolus arising from the lateral sinus, and that surgical intervention is, therefore, not necessarily urgent.

On the other hand, at the onset of a severe acute, but generalized upper respiratory tract infection, it is not unusual to find viable organisms in the blood, gaining entrance perhaps by way of infected capillary thrombi. As a rule, however, the blood cultures soon become sterile, even though the infection may extend to involve the middle ear or mastoid. The continued presence of viable organisms in the blood under such conditions must be regarded as very suggestive of a larger vessel's constantly feeding bacteria into the blood stream in large numbers. Even in such instances, however, and even despite the existence of obvious metastatic lesions, single blood cultures may prove sterile. All of these considerations point to the value of repeating blood cultures if they are to be interpreted correctly.

It is also of considerable interest and perhaps of some diagnostic value to note that as a causative agent the hemolytic streptococcus greatly predominates over all other organisms, being found in 88 per cent of our cases, the staphylococcus being responsible next most frequently, but only to the extent of 8 per cent. On the other hand, in our cases of septicemia not due to lateral sinus phlebitis, although the streptococcus still plays the chief role, it is only to the extent of 49 per cent, while the staphylococcus is concerned in 28 per cent of the cases. One, therefore, comes to expect the isolation of the hemolytic streptococcus from the blood of a case suspected of having lateral sinus phlebitis secondary to mastoiditis, and if some other organism is found, it demands special effort in searching for a different portal of entry. In this connection it is also of interest to point out the variation in mortality from septicemia when produced by lateral sinus phlebitis and when secondary to some other focus. The explanation probably is due to differences in the ease with which portals of entry may be diagnosed, approached surgically, and eradicated.

When there is bilateral otitis media with also obvious or suspected bilateral mastoiditis and symptoms indicative of lateral sinus phlebitis, it, of course, becomes extremely important to be certain on which side the phlebitis is present to avoid the mistake of tying off a normal jugular vein and incising a normal lateral sinus when thrombosis is developing on the opposite side. Of particular value in this connection is the Queckenstedt test, and comment should be made concerning its diagnostic value. In our summary we note that it was positive in 30 of the 35 instances (that is, in 86 per cent of the cases), questionable in 2 cases, and negative in 3. Despite these figures, there was a time when one of us in particular (A. F. H.) was very skeptical as to its value. This skepticism was due to difficulties in interpretation, the result of a number of facts. In the first place, difficulties were often encountered in

*We use the term "septicemia" to designate the state existing when viable organisms are present in the blood in association with other clinical evidences of severe infection.

performing the test, one of which was a failure on the part of the patient (usually because of a young age) to refrain from crying long enough to permit us to obtain a satisfactory base line reading of the spinal fluid pressure. Proper sedation and patience should overcome such a difficulty. Then also the position of the patient may sometimes affect the results, as we have on several occasions failed to see registered a rise in the spinal fluid pressure when compression of the jugular vein undermost was attempted (the patient was, of course, lying on one side at the time of lumbar puncture), being easily able to demonstrate patency of that side when the position of the patient was so changed that the vein in question became uppermost. Then, too, not infrequently early in the course of lateral sinus phlebitis, although sepsis was obviously present, there was not sufficient thrombosis to occlude the venous channel, and the Queckenstedt was, therefore, negative. Such negative findings should have been expected, however, early in the course of the infection, and we do not now feel that surgical intervention is contraindicated because of a negative Queckenstedt, if in all other respects the picture is that of sepsis due to mastoiditis and lateral sinus phlebitis. This is true particularly when there is but unilateral mastoid involvement. And, finally, during the period of just one year, three instances of a positive Queckenstedt test were encountered under circumstances which made us conclude that some cause other than a septic clot was responsible. In all three instances the left side was involved. In one, despite recovery without ligation of the jugular vein or incision of the lateral sinus, there was reason to believe from the operative findings at the time of mastoidectomy and from the later clinical course that the sinus was involved, but that the clot was either sterile or that infection subsided without drainage; in one the x-ray revealed a much smaller sinus on the left side at a time, fortunately, when the left mastoid was not under suspicion and when no doubts as to the involvement of the right mastoid existed;* in the other case there was doubtful visualization of a left lateral sinus, while a well developed sinus was visible on the right. These facts, (1) that there may be anatomical variations in the size of the lateral sinus,[1] and (2) that thrombi may be sterile, or become sterile without operative intervention, have to be considered in the interpretation of the Queckenstedt test.

Clinical Courses.—It will be noted from the summary that in 22 of the 57 cases reported upon there occurred rather rapid recovery following the operative procedure which we have come to regard as necessary: that is, simple mastoidectomy with ligation of the jugular vein and incision of the lateral sinus. Occasionally a septic fever with daily 10° F. fluctuations would cease almost immediately, so that after just 48 hours a normal temperature would result. Very often, however, a week or ten days would elapse before the fever subsided, and not infrequently after a week or more of normal temperature, an occasional temperature "spike" would occur, sometimes associated with a chill. In such instances, the temperature would usually rapidly return to normal, and generally no cause for it was ascertained. Sometimes, however, it could be attributed to manipulations necessary in dressing the wounds or changing packs. In 12 instances early death followed operative interference, while in 7 cases death occurred after a prolonged postoperative period, when perhaps for some time hope had been held for eventual recovery. In 16 cases recovery occurred only after prolonged illness, usually with one or more complications. *Charts 1, 2* and *3* are illustrative of such clinical courses.

Metastatic lesions as complications were noted in 26 cases (43 per cent), and it is interesting to comment on the fact that when joints were involved a certain diagnosis could not sometimes be made without diagnostic aspirations of the joints. More than half of the joint infections subsided spontaneously, that is, without repeated aspiration or drainage. In general, however, we have come to feel that when joint symptoms have persisted for more than two weeks, it is unlikely that such spontaneous recovery will take place. We have, however, noted one instance in which such spontaneous recovery followed after a month of involvement.

The incidence of meningitis and of central nervous system symptoms should also be discussed. A frank disseminated meningitis occurred in 10 cases (16 2/3 per cent), all of which terminated fatally. In 5 instances pleocytosis without organisms growing on culture occurred, 4 of the cases recovering. In the fatal case no lumbar puncture immediately preceding death was made, and the symptoms at that time suggested very strongly disseminated

*This apparent x-ray finding was later verified at autopsy.

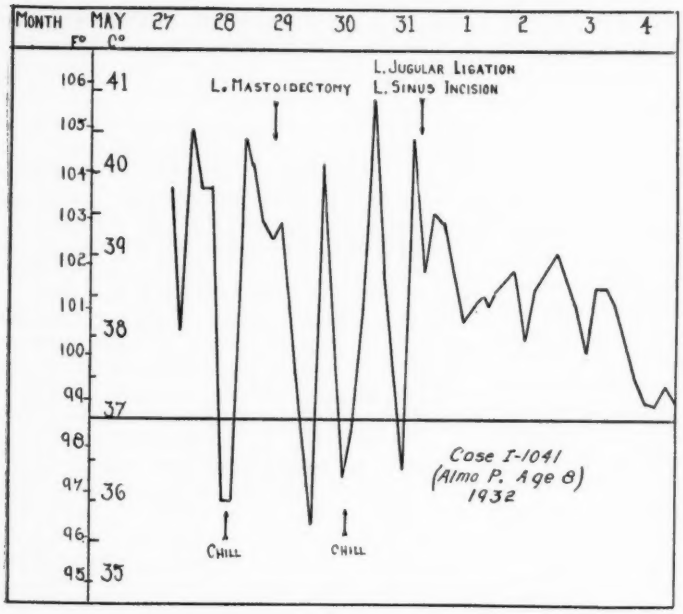

Chart 1
Case illustrative of uncomplicated rapid postoperative recovery.

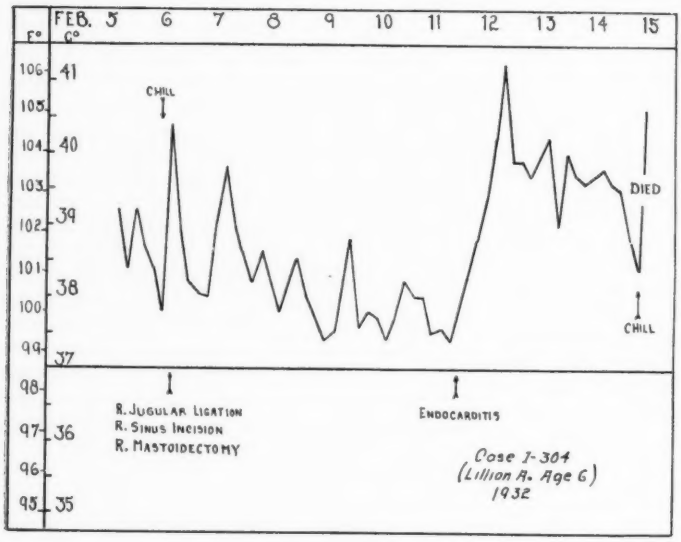

Chart 2
Case illustrative of development of rapidly fatal postoperative complication.

meningitis, and probably organisms would have grown from the spinal fluid at that time.

At some time during the postoperative course symptoms or findings thought very suggestive of brain abscess were noted in 6 cases, but rather unexpectedly in not a single instance in which attempts were made to locate such abscesses was one found, and with one exception these patients recovered, and the subsequent clinical courses tended to exclude the possibility of abscess. Also, no abscess was noticed in any of the 11 fatal cases coming to necropsy.

The persistence postoperatively of papilledema frequently caused differences of opinion as to its significance and therapeutic indication. It was usually the feeling of the neurosurgical staff that in such cases lumbar punctures should not be done to reduce spinal fluid pressure, because of the danger of the development of a fatal pressure deformity if a posterior fossa abscess were the cause of the persistent choked discs, whereas the pediatric and otolaryngological staffs usually recommended repeated spinal punctures. In reference to this important question we think it important to call attention to the facts that (1) the only two cases of optic atrophy noted occurred in cases in which therapeutic lumbar punctures were not performed, and (2) although brain abscess was frequently suspected, it actually had not developed in any one of our 60 cases. We therefore,

for the present at least, feel that it is better clinical judgment to perform repeated spinal taps if papilledema with increased spinal fluid pressure persists, and if the presence of a brain abscess is merely a possibility.

Descriptions of some particularly unusual cases should be included, because they bring out forcefully the difficulties encountered in interpreting therapeutic results.

Case 1.—J. J., a boy of 3 years, developed an initial otitis media on the right side on January 1, 1936. He developed a high fever, and was admitted to the hospital on January 22, 1936, with tenderness over the right mastoid, but with the right ear drum still intact. X-ray of the mastoid was indeterminate. The leukocyte count was 25,000, with slight left shift. After a sustained temperature around 105° F. for a week, during which time the daily blood cultures continued to be positive for *Streptococcus hemolyticus,* and during which time the spinal fluid, while remaining sterile, showed a cell count averaging 50 per cubic millimeter, the cells being chiefly polymorphonuclear leukocytes, a simple right mastoidectomy was performed. Pus and pyogenic membrane were found in the antrum and cells. The jugular vein was found thrombosed to such an extent that a ligature could not be placed low enough to be below the thrombosis. The lateral sinus wall was definitely thickened, and there was a perisinus abscess. Although this boy had positive blood cultures for the first nineteen consecutive days, he made an uncomplicated recovery following the mastoidectomy and incision of the lateral sinus, at no time developing metastatic lesions. The Queckenstedt test in this case was frankly positive, and papilledema of 2 to 3 diopters was noted preoperatively. At all times this boy failed to look

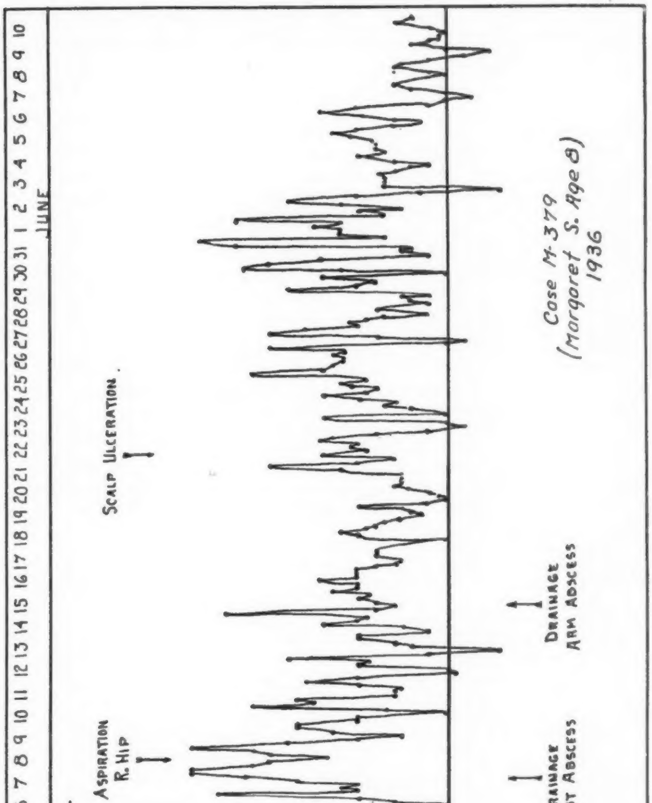

Chart 3

Case illustrative of eventual recovery despite prolonged postoperative sepsis due to development of multiple metastatic lesions.

as sick as one would have expected from examination of his temperature chart and his laboratory findings.

Case 2.—I. V., a girl of 5 years, developed bilateral otitis media following upper respiratory tract infection thought to be influenza. Five weeks previous to hospital admittance, on May 28, 1936, a septic temperature developed and persisted. On admittance there was a purulent discharge from the right ear, with the left drum intact. There was tenderness over the right mastoid. X-ray indicated mastoid involvement on the right side, the left showing very little. Bilateral papilledema of 2 diopters was present, and the Queckenstedt test, which was one of the doubtful ones, showed a rise of only 30 millimeters on either side. In other respects the spinal fluid was normal. A single blood culture was negative, and the leukocyte count was 12,000, without a left shift. At the time of right simple mastoidectomy on May 28, 1936, where the lateral sinus should have been there was simply pus and granulation tissue, apparently with complete obliteration of the sinus at that point, with a black area of tense dura adjacent, which was the size of a quarter. Following simple mastoidectomy and drainage of the perisinus abscess without jugular ligation, the temperature quickly became normal, and the papilledema disappeared, and the tense dura became dimpled and suggested strongly that a spontaneous drainage of a localized meningitis, or perhaps of a cortical abscess, had occurred.

Case 3.—E. C. was a boy of 13 years in whom a primary attack of otitis media involving the left side occurred about April 12, 1936. He was admitted to the hospital on April 22, 1936, with tenderness over the left mastoid, draining left ear, septic temperature with chills, a leukocyte count that varied from 11,000 to 17,000, with slight left shift, a positive blood culture for *Streptococcus hemolyticus,* and bilateral papilledema which increased until it became 5 diopters. The spinal fluid pressure was so increased that it exceeded 750 mm. water and the fluid overflowed the Queckenstedt tubes. There were only eight cells, and the fluid was sterile. Left simple mastoidectomy was performed on April 22, 1936, the day of admission, a perisinus abscess being found. The lateral sinus was not incised, however, nor was the jugular vein ligated. Septic manifestations promptly disappeared following this operation, but papilledema increased, and when the mastoid was reopened on May 16, 1936, a bulging dura was noted. By this time he had developed a left sixth nerve weakness, an inconstant nystagmus, was lethargic, and frequently complained of headache. The spinal fluid pressure had gradually decreased, however, but the Queckenstedt test became frankly positive on the left, and suspiciously positive on the right. Repeated lumbar puncture, while apparently successful in keeping spinal fluid pressure down, failed, however, to have any effect on the degree of papilledema. Ventriculograms showed no deformity, and finally to preserve vision, a subtemporal decompression was made. In this case there was no satisfactory explanation for the continued papilledema.

Case 4.—H. C., another very unusual case, has already been reported in detail by one of us (A. J. C.[2]).

Preoperative and Postoperative Supportive Treatment.—In the end, we must depend for a favorable outcome on the body's own resistance to the streptococcic infection. The operative procedures are designed merely to provide surgical drainage of an area of infection, and to eradicate large portals of entry of bacteria into the blood stream. In addition to the proper operations, we have been impressed by a need both preoperatively and postoperatively of adequate general supportive treatment. With the proper administration of whole citrated blood, isotonic sodium *r*-lactate, lactate-Ringer's solution, and dextrose solution, dehydration, ketosis, acidosis, anemia and hypoproteinemia may easily be prevented or relieved. The importance of these measures cannot be over-emphasized. The specific need of a measure for increasing the body's resistance to the streptococcus, however, is still keenly felt. Occasionally following the intravenous injection of mercurochrome and of whole citrated blood, especially when the latter was obtained from members of the immediate family who had recently recovered from streptococcic infections, results occurred which were suggestive of specific bactericidal or immunizing effects. For the most part, however, such measures failed to show any decided immediate influence on the clinical course. We are looking forward at this writing to the effects which might be obtained by the use of "prontosil" and "prontylin," and it seems not impossible to expect from recent clinical reports[3] and from some of our own recent experiences with streptococcic infections, that these substances may prove to be of great value in controlling septicemia and the development of metastatic foci during the most dangerous preoperative and postoperative periods of lateral sinus phlebitis.

Mortality.—In considering the results of the entire group, a number of factors must be considered. In the first place, of the 21 deaths (35 per cent), 3 occurred in patients unoperated, the diagnosis not being made in two instances, and death occurring in the other case before any operation could be performed. One patient, with bilateral sinus thrombosis and extensive lung abscesses and other metastatic foci, died on the operating table. Another died a few hours following operation, the latter not being completed because of the patient's moribund condition. Another had disseminated meningitis at the time of operation. In all fairness, therefore, 6 of the 21 deaths should be excluded in the evaluation of the results of operative treatment. The mortality in the re-

vised group of cases then becomes 15 out of 54, or 27.8 per cent. In one year (1932) of the 8 cases seen, 6 died, 5 of these succumbing to meningitis, the other to endocarditis and pericarditis (see *Chart 2*). One of the two cases recovering had a spinal fluid cell count of 20, the fluid being sterile, while in the remaining case the spinal fluid was not examined. For this year then there seemed to be a striking tendency for the organisms to invade the meninges. That strains of hemolytic streptococci were of unusual virulence in 1932, however, is not indicated by other streptococcic infections of that year, which, comparatively speaking, were generally less common and less fatal than in preceding and subsequent years. On the other hand, in 1926, 6 cases were noted with 4 deaths, the fatalities, however, resulting from meningitis in only one instance, and from pulmonary and cardiac complications in the other three.

Of the 18 cases with histories of long-standing or frequently recurring otitis media before the development of lateral sinus symptoms, 7 died, a mortality percentage of 39, which is almost identical with the mortality for the entire group. Of the 10 cases of scarlet fever, 4 died, also a comparable mortality percentage.

More enlightening is the fact that the great majority of the fatalities in the group operated upon had already developed metastatic foci before the time of operation, and this fact is the basis for the oft-made valuable "teaching" statement of Dr. Harry Lyman, "If you wait for such a cardinal symptom as metastatic infection to diagnose lateral sinus phlebitis complicating mastoiditis, you are waiting for a fatal symptom!"

It is probably chiefly to the earlier recognition of the presence of this serious complication that we owe our reduced mortality of the past three years (2 cases out of 13 cases operated upon, or 15.4 per cent, if we exclude the case admitted to the hospital with meningitis). The more effective operative procedures and the more adequate preoperative and postoperative supportive treatment probably also played some role in this reduced mortality. It is quite apparent, however, that comparably low mortality rates over a space of from one to three years can also be noted in periods other than the last three years.

CONCLUSIONS

Obviously no sweeping conclusions can be made from this study, but we have developed a definite realization of the value of certain findings in the diagnosis, and a fairly clear idea of proper management.

All cases of otitis media and mastoiditis should be regarded as potential cases of sinus phlebitis. When clinical symptoms arise which make us suspect this complication, we should take advantage of the help which blood cultures, fundus examinations and spinal fluid examinations, which include the Queckenstedt test, may give us in arriving at an early diagnosis. If all signs point without question to lateral sinus phlebitis, the operative procedure should be ligation of the internal jugular vein if the ligature can be placed below the thrombus, then complete clearing out of all mastoid cells with uncovering of the sinus, and incision throughout its diseased portion. If involvement of the lateral sinus is uncertain, simple mastoidectomy should be done, during which the sinus should be carefully inspected. If improvement follows, well and good. If sepsis continues, even in the face of a negative Queckenstedt test, jugular ligation and sinus incision should then be performed, provided, of course, no other cause for the continued sepsis can be found.

At all times supportive treatment with parenteral fluid therapy to relieve or prevent dehydration with chemical changes should be carried out. Transfusions should be included.

If papilledema persists after operation, frequent lumbar punctures should be done to note the effects of so relieving intracranial pressure. If inadequate, study by ventriculogram for abscess and exploration, if indicated, should next be considered. Finally, subtemporal decompression should be done to preserve vision in those few cases of continued papilledema without abscess.

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DISCUSSION (*Abstract*)

Dr. John J. Shea, Memphis, Tenn.—The two usual fatal endings of acute mastoiditis in children are the result of sepsis or acute meningitis. The former is the eventuality of thrombophlebitis, unless the condition is diagnosed early and properly treated.

The two most recent series reported of acute mastoiditis with intracranial complications were Fraser and Halliday, 139 (15 per cent) intracranial complications among 891 consecutive cases of acute mastoiditis from the Royal Infirmary of Edinburgh during the past fifteen years, of which 60 (6 per cent) ended fatally. Boies reported 300 cases of acute mastoiditis from his private practice and the otolaryngological service of the University of Minnesota Hospital, of which the incidence of extradural inflammation was 35 per cent.

The most significant part of Dr. Hartman's statistics, to an otolaryngologist, is the reduction of his mortality during the past three winters from 37 per cent to 21.4 per cent, and quoting from his statistics, he thinks this is due to (1) earlier recognition, (2) better operative methods, (3) better pre- and postoperative supportive treatment (fluids, blood, and so on).

This shows a better cooperation between the pediatric and otological service of his institution.

In your Chairman's address, the statistics are for a Southern city, and the insidious advice of trying x-ray therapy in acute mastoiditis will lead to more cases of thrombophlebitis of the lateral sinus or meningitis if followed in our more rigorous climates.

I agree perfectly with all of Dr. Hartman's conclusions and only wish to add that in the South the only disease that must be ruled out is malaria, for I have seen rigor and high fever startle us in a postoperative case, to find that our anesthetic had driven into the general circulation a quiescent malaria.

The following chart may be used to advantage in the early diagnosis of thrombosis:

DISEASE	SPINAL FLUID	CELLS	ORGANISMS
Otitic Meningitis	Cloudy or purulent	Polynuclear Mononuclear Small number	Streptococci, Diplicocci, Streptococcus mucosus, Influenzal bacilli
Brain Abscess	Either cloudy, purulent or clear	Polynuclear Mononuclear Large number	No bacteria
Tuberculous Meningitis	Purulent, cloudy, or opalescent	Mononuclear	TB bacilli or negative
Epidemic Meningitis	Cloudy or purulent	Mononuclear 1 Polynuclear 2 Mononuclear 3	Diplococcus intracellularis
Sinus Thrombosis and Septicemia	Clear	No cells	Nothing

THE MANAGEMENT OF BLOOD STREAM INFECTION WITH SPECIAL REFERENCE TO IMMUNIZED BLOOD TRANSFUSIONS*

CASE REPORTS

By ELBYRNE G. GILL, M.D., F.A.C.S.
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If all the cases of blood stream infection presented the classical textbook symptoms, the subject would be of little interest. However, each case presents some variations which make the diagnosis and treatment a difficult problem. Some of the problems are as follows:

(1) In cases where thrombosis of the sigmoid sinus is complete should the jugular vein be ligated?

(2) Where there is complete thrombosis of the sinus, should all the clot be removed in order to secure free bleeding?

(3) What surgical procedure should be used in dealing with the vein: (a) ligation, (b) ligation and division, or (c) ligation resection?

(4) Do the vein and sinus function after ligation and compression?

(5) What place, if any, has chemotherapy in the medical treatment?

(6) What place has blood transfusion in the medical treatment?

(7) What place has bacteriophage therapy?

(8) What place has non-specific protein therapy?

(9) What place has immune serum therapy?

(10) What is the value of anti-streptococcic serum?

The diagnostic aspects of blood stream infection will be discussed only in connection with the treatment. It will be presumed that a thorough differential diagnostic study has been completed, and we are dealing purely with an infection of the blood with all that it implies.

STUDY OF THE BLOOD

In[1] every suspected case a complete blood count should be made daily. It tells us whether the disease process is going or coming. Ordinarily the leukocyte count is parallel with the

*Read in Section on Ophthalmology and Otolaryngology, Southern Medical Association, Thirtieth Annual Meeting, Baltimore Maryland, November 17-20, 1936.

severity of the infection. A Schilling hemogram is of much greater value in determining the presence of a severe systemic infection. Eosinophils disappear from the blood in severe infections and their reappearance is the earliest favorable sign. If other complications have not occurred, there should be a rapid increase in the red cells and hemoglobin after the infection is eliminated from the blood stream. Blood culture should be made early in the course of the disease. Bacteria may occur in the blood intermittently, which makes it important to take two or more cultures at intervals of one or two days. Many observers have emphasized the importance of taking blood for culture from a vein draining an infected area where possible.

BACTERIOLOGY

A bacteriological examination of the primary focus of infection, either the ear or mastoid, and culture, should by all means be made at the onset of the disease. The possibility of septicemia's developing may be estimated sometimes by the knowledge of the nature of the initial infection. Hemolytic streptococcus is the organism most frequently found.

TREATMENT

The treatment is both surgical and medical. The surgical treatment consists essentially of a thorough mastoid operation, simple or radical, depending upon the indications. Since it is not always possible to differentiate by symptoms and laboratory tests a sinus clot from a bacteremia, one is justified in performing a mastoid operation and freely exposing the sigmoid sinus. Slightly more than the width should be exposed for inspection and compression if it is decided upon later. The appearance of the bony sinus plate is not to be relied upon. Oftentimes we find a sinus thrombosed or abscessed, yet the bony plate was apparently sound. The mastoid emissary should be exposed if present; no other surgery is done. The wound is left open and particular care should be used in packing it. There is little likelihood that the sinus will become infected if the packing is not placed against it. If the septic symptoms become more pronounced and there is definite evidence of thrombosis, the sinus should be drained or compressed.

After the sinus has been opened and compressed, if there is continued evidence of advancing sepsis, despite vigorous medical treatment, the jugular vein should be ligated, not divided or resected. In case of complete thrombosis, the questions arise: (1) Should the clot be curetted until free bleeding occurs from each end? (2) Should the jugular be ligated before opening the sinus? We do not attempt to remove all of the thrombus from the sinus in order to secure free bleeding. The thrombus is nature's attempt to stop the infection. When the thrombus is removed and free bleeding occurs, gauze plugs have to be used. Gauze plugs are objectionable. (1) There is a foreign body in an infected field adjacent to the dura with the possibility of producing trauma to the brain and possibly meningitis or an abscess. (2) There is the problem of removal. It is usually five or six days before these plugs can be removed.

It is our purpose to open the sinus for about one inch and drain by use of a soft rubber catheter. Never use curettes or any metallic instruments. The opening in the sinus is packed with iodoform gauze to prevent sudden bleeding if there is breaking down of the thrombus. The packing can be removed in two or three days instead of the usual five or six days and this lessens irritation of the brain and general toxemia.

MEDICAL TREATMENT

With the advent of blood transfusions and other intravenous methods, physicians and surgeons have been searching for something specific in combating infections of the blood stream. Many chemicals[2] of alleged value have been given wide publicity, but at the present time there is no chemical agent possessing the curative effects of arsphenamine and neo-arsphenamine in the treatment of syphilis and other spirochetal infections, and of quinine in the treatment of malaria. The most effective medical treatment may be listed in the following order:

(1) Blood transfusions
(2) Intravenous glucose and saline
(3) Anti-streptococcic serum
(4) Non-specific protein therapy
(5) Bacteriophage

BLOOD TRANSFUSIONS

Transfusion of human blood is no longer considered a dramatic measure, nor is its use confined to patients in the fatal stage of illness, but is now employed by the alert surgeon preoperatively, sometimes during operation, more often postoperatively. The general acceptance of this

mode of therapy and the frequency of its administration demands serious consideration of the methods of transfusion, the preparation of the donor, and the possibility of unfavorable reactions.

TYPE OF TRANSFUSIONS

Whole natural blood and modified or citrate method. The whole method is preferable. Reactions are fewer than by the citrate method. A whole blood transfusion is valuable in the treatment of septicemia, and supplies the patient (1) with fresh leukocytes for the elaboration of bactericidal substance if the patient's leukocytes are exhausted and incapable of immunologic response, and (2) for the purpose of supplying the patient with complement.[2] Transfusions should be given at frequent intervals. The well being of the patient determines the frequency of the transfusions, and not the hemoglobin content or white cell count. Small amounts of blood should be given at a time, not more than 150 c. c. So long as there is definite clinical evidence of sepsis, the blood transfusions should be repeated, irrespective of any laboratory findings.

SELECTION OF DONOR

The surgeon and technician must exercise the utmost precaution in the selection of a donor and the matching of the blood to avoid the mortifying error of using a donor not of the patient's group, thus producing a serious reaction and possibly death. The following points should be considered in the selection of a donor:

(1) Use young adult donors

(2) Use different donors for each transfusion

(3) Cross match patient and donor each time transfusion is given

(4) Use fasting donors when suspicious of protein sensitivity

(5) Donors should be free of constitutional disease such as syphilis, malaria, and asthma.

TYPING

The very careful matching of the blood of patient and donor is required in order to avoid reactions. Jansky and Moss have classified human blood into two groups, but the final selection of a donor must be left to a well trained laboratory technician and surgeon. Kolmer[2] and others, in the interest of safety and simplicity, recommend dropping Moss and Jansky's classifications and employing only that of Landsteiner.

Landsteiner Group A corresponding to II of Jansky

Landsteiner Group B corresponding to III of Jansky

Landsteiner Group AB corresponding to I of Moss and IV of Jansky.

DANGERS OF BLOOD TRANSFUSIONS

Stetson classifies reactions as

(1) Hemolytic

(2) Proteolytic

The hemolytic are those resulting from incompatibility between the bloods of patient and donor due to mistakes in grouping, when the patient has an active hemolytic agent breaking down the cells. This condition may occur in pernicious anemia, purpura, hemolytic jaundice, leukemia and sepsis.

The proteolytic[4] consists of (1) febrile reaction, where the protein contents of donor's blood produces the reaction. (2) Protein reaction which shows dermal reaction of true allergic phenomena with or without systemic manifestations. (3) Anaphylactoid. Some of the reactions are of the true protein type and possibly some are due to minor agglutinins.

TRANSFUSIONS OF IMMUNIZED BLOOD

Immunized blood consists of:

(1) Non-specifically immunized blood

(2) Specifically immunized blood

(3) Immunized blood from a donor who possesses immunity through recovery from blood stream infection.

Specifically immunized blood is prepared in the following manner: A compatible donor is selected and is given at weekly intervals a vaccine prepared from the bacteria isolated from the patient's blood stream, beginning with 50,000,000 and increasing to 250,000,000. Usually one week following the last injection, the transfusion is given. Transfusions by this method require the aid of an expert laboratory technician and are time-consuming. The patient may not live four or five weeks.[5] This method has been described and advocated by Brody, Crocker, and others. More recently Brody and Stephenson[6] have advocated non-specific immunized transfusion. This consists of giving the donor 50,000,000 to 75,000,000 typhoid vaccine by intravenous injections. This usually produces a shock in one hour, which is characterized by chills, fever and leukocytosis. Seven hours later, after

acute reaction has subsided, the blood transfusion is given. The only objection to this method is the unpleasant reaction in the donor.

COMMENTS

The surgical and medical treatments are interrelated and the essential features can be briefly given in one paragraph. The surgery consists of adequate drainage of the primary focus of infection and the obliteration of areas of thrombophlebitis.

The desideratum in medical treatment is some chemical agent which will disinfect fixed tissues and the blood when given in non-toxic amounts intravenously or intramuscularly. The nearest approach to this ideal is a blood transfusion from a compatible convalescent donor. The surgeons of the hospitals of each city should make a permanent record of patients who have recovered from blood stream infection and secure permission for grouping, thus making them available donors for emergency transfusions. The duration of immunity in compatible convalescent donors is not known. We have never observed a patient having a recurrent blood stream infection of the hemolytic streptococcus, nor have we reviewed reports in the literature.

When compatible convalescent donors are not available, and the infection is progressing rapidly, a non-specific immuno transfusion should be given. Preparation of a specifically immunized donor should begin and be used if the infection persists four or five weeks.

Otologists universally accept blood transfusion as a valuable aid in combating infection. The primary purpose of my paper is to make a plea (1) for more general use of immunized blood transfusion by one of the methods outlined; (2) for more general use of anti-streptococcic serum for its prophylactic and curative value. The serum should be given early in the course of the disease and repeated daily for six doses. It may be given intravenously or intramuscularly; (3) for generous utilization of intravenous glucose and saline by the continuous drip method, giving as much as 3,000 c. c. in twenty-four hours.

Bacteriophage is difficult to secure for hemolytic streptococci, but if available, it may be given subcutaneously or intravenously.[3] Non-specific protein reactions are helpful if given early while the bone marrow has the capacity for favorable reactions. These reactions may be produced by the use of typhoid bacilli, sterilized milk or autogenous vaccine. Intravenous injections of neoarsphenamine are of value in selected cases. Cadham[7] reports a series of one hundred patients treated with human serum. The serum is used in place of whole blood for reactivation of complement.

CASE REPORTS

Notes on three cases treated surgically and with immunized transfusions are as follows:

Case 1.—G. V., aged 20, white male, entered the hospital March 1, 1936, complaining of pain in the left ear, sore throat, and nasal discharge, following an attack of influenza of two weeks' duration.

His tonsils were acutely inflamed. The frontal sinuses were clear. Both antra were dark.

Three days after admission, acute otitis of the right ear developed, necessitating myringotomy. Despite active local and general treatment, the patient's general condition progressed unfavorably as shown in laboratory and clinical tables. On March 11 bilateral mastoidectomy was performed. The left mastoid was sclerotic, but definitely involved; the right mastoid pneumatic and broken down. The patient continued to manifest evidence of sepsis and one week following mastoidectomy a severe chill, elevation of temperature and positive blood culture definitely fixed the guilt in the blood stream. All the recognized tests failed definitely to determine the portal of entry of the infection. The right sinus was freely exposed and found healthy, then the left, which was covered with granulations, and upon opening the sinus a mural clot was found. The sinus was compressed. Improvement followed this procedure. During the following two weeks seven metastatic skin abscesses developed, which were drained surgically. Seven blood transfusions were given as shown in the chart. The seventh one was from a boy, 10 years of age, possessing immunity to this infection since he had recovered from a similar infection three years before. All septic symptoms promptly subsided following this transfusion and recovery was uneventful and permanent.

Case 2.—Patient L. R., aged 30, came to the hospital March 13, 1936, complaining of pain in the left ear and mastoid area of two weeks' duration. The ear infection followed an attack of scarlet fever.

There was profuse discharge from the left ear. The right ear was normal. Both maxillary antra were dark. Physical examination was negative. The clinical, laboratory and x-ray findings reveal positive evidence of left mastoid suppuration.

On March 14 a simple mastoidectomy was done. The sinus plate had been destroyed by disease, thus exposing the sinus. The patient had persistent pain in the operative area, requiring opiates for relief. On the sixth postoperative day, the temperature recorded 105°, associated with an increased leukocyte count and chill. On the seventh day, the temperature again recorded 105°. At this time the lateral sinus was exposed and compressed after free bleeding occurred from the bulbar portion. Culture made from the blood in the sinus are positive for hemolytic streptococcus. The patient continued to manifest evidence of sepsis (see chart for the temperature curve and laboratory findings). The medical treatment consisted of free utilizations of anti-streptococcic serum,

Case I	Amt. Transfusion, c. c.	W.B.C.		R.B.C.		Hemoglobin		Shift				Temp.		Blood Culture	Progress
								Before		After					
		Before	After	Before	After	Before	After	Stap.	Poly.	Stap.	Poly.	Before	After		
March 12	180	12,250	12,750	4,240,000	4,850,000	92	91	47	42	69	16	105.4	104.8		Septic
March 14	210	10,050	9,990	4,540,000	5,390,000	95	100	83	9	80	18	104.6	104.2		Septic
March 16	125	14,650	9,650	4,990,000	4,950,000	99	99	62	22	49	37	104	102.4		Septic
March 18	125	10,600	14,950	5,370,000	4,870,000	101	100	50	37	39	45	103.6	104.2	+	Septic
March 20	120	21,750	24,850	4,400,000	4,780,000	94	97	33	35	45	46	103.2	102.4		Septic
March 23	120	22,500	14,500	4,180,000	4,480,000	96	96	45	46	38	49	101.4	102.6		Septic
March 26	100*	24,850	21,200	4,590,000	5,070,000	96	96	44	46	40	51	100.6	99.4		Recovery

*Donor, boy 10 years old, had recovered from similar infection three years previously.

Case II															
March 22	210	19,200	13,350	4,100,000	3,870,000	85	84	45	42	47	34	103	104.8	Neg.	Septic
March 25	130*	12,700	8,550	4,900,000	4,550,000	90	87	30	33	36	43	102	101.6	Neg.	Septic
April 4	120*	10,050	10,350	3,860,000	3,820,000	81	81	44	25	33	32	99.2	103.2	Neg.	Septic
April 6	100	10,350	16,000	3,820,000	4,710,000	81	90	33	32	35	40	104.2	100	Neg.	Recovery

*Donor previously recovered from erysipelas.

Case III															
Sept. 28	210*	12,450	13,100	4,380,000	4,250,000	61	67	34	48	30	34	102	100	Neg.	Recovery

*Donor given 50 million dead typhoid bacilli intravenously seven hours prior to transfusion.

glucose and saline and blood transfusion from a compatible convalescent donor (see chart).

Case 3.—Patient C. H., aged 17, came to the hospital September 25, 1936, complaining of pain in the left ear and mastoid area of one week's duration. The ear infection developed as a sequel of tonsillitis.

The right ear was normal. The canal of the left ear contained a thick purulent discharge indicating osseous destruction. Tenderness on pressure was elicited over the entire mastoid process (see chart for blood, temperature, pulse record and laboratory findings). The day following admission, the clinical symptoms of mastoiditis became more pronounced with temperature elevation to 104° and definite x-ray findings. A complete simple mastoid operation was done. September 26, 1936, the entire mastoid process showed marked involvement with suppuration. The sinus and dural plates were not disturbed, as they presented a normal appearance. The culture from the mastoid wound showed a mixed growth of pneumococcus and streptococcus. The temperature postoperatively was of a typical septic character, ranging from 99 to 102.2°.

Following a transfusion of non-specific immunized blood, the septic symptoms promptly subsided and the temperature came to the normal level. This patient did not have a positive blood culture, but the septic symptoms definitely indicated a beginning invasion of the blood stream, all of which disappeared promptly following the immunized transfusion.

CONCLUSIONS

The administration of immunized human blood transfusion deserves a rightful place with insulin, diphtheria antitoxin and neoarsphenamine as a conqueror of disease, benefactor of mankind, and a life-saving measure.

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DISCUSSION (*Abstract*)

Dr. John A. Kolmer, Philadelphia, Pa.—I agree with Dr. Gill that the great majority of blood stream infections complicating mastoiditis and its associated lesions are due to hemolytic streptococci belonging to Group A. By serological tests these have been divided into 11 to

20 types and any of them may cause not only acute upper respiratory tract infections, including mastoiditis and sinus thrombosis, but scarlet fever, puerperal sepsis, cellulitis, lymph-adenitis, and so on. Indeed we are not now privileged to think that scarlet fever and erysipelas are due to specific types of streptococci, but rather that these may be caused by any member of Group A of hemolytic streptococcus.

I emphatically advise the practice of routinely culturing all cases of mastoiditis on plates of blood agar at the time of operation. As a general rule the bacteriologist can submit a preliminary report in 24 hours. If hemolytic streptococci are present in pure culture or in large numbers, I then advise the intramuscular injection of about 20 to 40 c. c. of concentrated polyvalent antistreptococcus antitoxin for prophylactic purposes, especially if thrombophlebitis has been found. We have long since learned of the prophylactic value of diphtheria, tetanus and gangrene antitoxin, but surgeons and obstetricians have been very slow in learning that concentrated antistreptococcus sera as now available appear to have definite prophylactic value in these surgical infections. At least we have obtained evidence to this effect in our experimental work with monkeys and dogs on streptococcus meningitis and septicemia. It is true that one does not wish to sensitize individuals unnecessarily by the needless administration of this serum but, in severe cases of mastoiditis and especially those complicated by lateral sinus thrombosis, I believe the indications for prophylactic immunization are far more definite than in the majority of individuals to whom tetanus antitoxin is freely given following injuries.

Since I am not a surgeon, it would be impertinence on my part to offer advice on the surgical management of blood stream infections complicating mastoiditis with or without sinus thrombosis. But as a bacteriologist and immunologist, I find myself in entire agreement with the surgical management advised by Dr. Gill. That is to say, I strongly advise instituting promptly the best surgical drainage, but this requires the finest of surgical judgment, since great care is required to avoid the regrettable accident of opening up channels for the spreading of infection by surgical intervention. Therefore, I think that it may be inadvisable routinely to remove the clots, providing one may be reasonably certain that adequate drainage is provided. I can speak only of the principle involved, namely: the advisability of providing adequate drainage as quickly as possible with the least possible trauma or opening of new lymphatic and vascular channels.

From the standpoint of diagnosis I wish to urge blood cultures as soon as possible in all cases where septicemia is suspected. In my experience diagnosis cannot be safely entrusted to clinical manifestations alone, since septicemia can be present in the absence of the classical manifestations, and on the other hand it may be absent when fever and chills indicate its presence. There may be the result of toxemia from local infection alone; and when blood cultures reveal the presence of streptococci, prompt measures are required in treatment.

Next to providing adequate surgical drainage, I advise the prompt administration of concentrated antistreptococcus serum preferably by intravenous injection with proper precautions against anaphylactic shock. Everything in serum therapy points strongly to the fact that all immune sera possess more prophylactic than curative activity and that in treatment large doses are required as promptly as possible. Certainly we have long since learned this lesson in diphtheria but, in streptococcus infections, there is still a regrettable tendency to delay serum too long and to use it too timidly. A better policy is to give 20 to 50 c. c. of concentrated serum diluted with saline solution every 8 to 12 hours for at least the first two or three days in much the same manner as the administration of antipneumococcus serum is used in the treatment of lobar pneumonia.

Since it appears that the complement of the blood and possibly natural antibodies (especially the opsonins) tend to become exhausted in septicemia, there is a real place of value for blood transfusions in treatment as emphasized by Dr. Gill. My practice is to give 150 to 200 c. c. every two or three days, preferably by a direct method. The first one or two should always be given as soon as possible while antistreptococcus serum is being administered with the thought that the blood furnishes complement while the serum furnishes antibody.

Theoretically at least, an immune donor is to be preferred with the hope of furnishing not only complement but antibody as well. In this connection I advise using a compatible donor who has had scarlet fever or some other hemolytic streptococcus infection because as previously stated, all of these belong to Group A streptococcus with the chance of using a donor carrying antibody for the particular streptococcus infecting the patient.

Otherwise, it may be advisable to use the nonspecific type of transfusion mentioned by Dr. Gill, providing a compatible donor can be found who is willing to bear with the chill and fever following the intravenous injection of 50 to 100 million typhoid bacillus vaccine. The blood is taken several hours later upon the subsidence of the reaction and is believed by many to be superior to plain transfusions on the basis that it contains an excess of leukocytes and probably humoral immune substances of benefit to the patient.

Bacteriophage may be employed providing a sufficiently lytic one can be found for the patient's streptococcus which is ordinarily very difficult. It is also given intravenously, but I am personally not yet able to express an opinion of its value.

Unfortunately chemotherapy has at present little to offer, as intimated by Dr. Gill, because we have no chemical agent which can be depended upon to disinfect the local or fixed tissues which presumably continue to feed streptococci into the blood. But I am confident it will be eventually found if sufficient money and interested workers are available for the expensive and laborious researches required. At present we are greatly interested in a new pyridine compound produced by my colleagues and myself at the Research Institute of Cutaneous Medicine in Philadelphia, as it has been apparently more effective in the treatment of experimental hemolytic streptococcus infections of rabbits and in a small series of infected human beings than other agents we have employed. Otherwise, intravenous injections of neoarsphenamine may be tried as well as mercurochrome, metaphen or other mercurial compounds with the hope of reducing the bacterial population of the blood even though there is little hope of effectively disinfecting the fixed tissues and especially the areas of thrombophlebitis.

The treatment program is therefore a vigorous one, requiring daily arrangement for each individual patient, embracing as it does not only surgical drainage, but biologic therapy and, sometimes, chemotherapy as well,

in addition to intravenous injections of glucose, keeping the total fluid intake to 2,000 or 3,000 c. c. per day, relief of pain and restlessness, relief of abdominal distention, and so on. Under the circumstances one may easily overlook the importance of rest so essential to the welfare of the patient and, for this reason, the therapeutic plan for each day should be so arranged as to disturb the patient as little as possible.

Dr. Fletcher D. Woodward, University, Va.—Dr. Gill emphasizes the modern trend in the treatment of blood stream infections. The fundamental importance of adequate and prompt surgical drainage of the primary focus, combined with blood transfusions, has been well recognized for a long time, but it is comparatively recently that any progress has been made beyond those fundamentals by employing immunized blood and human serum.

In phlebitis and thrombosis of the lateral sinus, we have a problem that varies with each patient. In regard to some of the controversial points, I should like to state my procedure briefly and my reasons therefor.

The jugular vein is exposed and ligated, preceding the mastoid operation when evidence is strongly suggestive of lateral sinus involvement because of the opportunity of operating in a clean field, of preventing septic emboli through the jugular during subsequent manipulation of the sinus, and because it gives an opportunity of placing a drain at this crucial point in the carotid sheath should infection be present in the vein, or should it subsequently occur. The transverse incision following the skin folds is negligible and ligation is all that is necessary unless phlebitis and thrombosis are present. Then resection and drainage are done. When there is much doubt as to involvement of the sinus the mastoid and sinus should be explored first, and our subsequent procedure in regard to the jugular determined. The sigmoid sinus should be opened for adequate inspection and drainage. In some cases all of the thrombus is turned out and free bleeding obtained; in more extensive thrombosis, no attempt is made to remove all of the thrombus beyond evident disease, because that portion of the thrombus is sterile and protective, while in those cases of localized phlebitis without thrombosis, mere incision, and compression above and below to confine hemorrhage, will be all that is necessary. Only when an extensive and infected thrombus is found down to the bulb do we subsequently explore the jugular vein in the neck. It is quite evident to all who have studied these cases how futile it is to establish definite rules and how important it is to rely on our surgical experience and judgment in the handling of each particular case.

In my opinion, there is no definite place today for chemotherapy, nonspecific protein therapy, bacteriophage, or either nonspecific or specifically immunized blood. We do use antistreptococcus serum, but results are both variable and questionable.

In the blood study the Schilling hemogram is more important than the total white count, for in a study of twenty of our cases, reported in 1930, the average count was 13,000, and in four of them it was below 10,000, so I do not agree with Dr. Gill in his statement that the leukocyte count parallels the severity of the infection.

Repeated blood cultures are important, but instead of the conventional 10 c. c. Dr. Friesner, at Mt. Sinai in New York, is employing 40 to 50 c. c. of blood for each culture with a very much higher per cent of positive cultures. Of course, bacterial cultures of the discharge from the ear should be taken as a routine when the case is first admitted to the hospital.

Repeated blood transfusions are most important and whenever possible convalescent donors should be employed. In addition to these, the use of convalescent serum by Baum, of Denver, is most interesting. He collects and stores the serum from all types of convalescent streptococcus infections, and by agglutination methods the most specific serum for the particular infection can be promptly selected and given intravenously in 40 to 50 c. c. amounts with most gratifying results. He has employed this method in well over a thousand cases with no untoward results, and I feel it would be wise if we should employ this method more widely, for any additional help along more specific lines in the treatment of these cases will be a big step forward. When dealing with staphylococcus blood stream infection, we feel it very important to have an early estimation of the patient's blood titer and to start toxoid, for we have found it to be of very real help in combating staphylococcus infection. Likewise the staphylococcus antiserum can be given to control the toxemia.

I congratulate Dr. Gill on the way he has brought this most important problem before us.

ACUTE HEMATOGENOUS OSTEOMYELITIS WITH ADJACENT JOINT INFECTION*

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Infection of a major joint is usually regarded as a grave complication, particularly when the infection arises from an area of osteomyelitis within an adjacent bone. Beekman[2] believes that hematogenous synovial infection with *Staphylococcus aureus* is rare, and that the joint is usually infected from adjacent osteomyelitis. In a series of two hundred and seventeen cases of acute and chronic osteomyelitis, Bisgard[3] found fifty-one infected joints, of which forty-two originated from adjacent osteomyelitis. Starr[15] states that the adjacent joint is more frequently infected by operation than by primary extension. Pearson[11] believes that the effusion in such a joint is at first serous and sterile, but will later become purulent if the case is neglected. Cofield[5] found it difficult to culture organisms from aspirated joint fluid, while Martin[10] says that positive demonstration of bacteria in the effusion is necessary before conclusions can be drawn. Kistler[9]

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has produced acute osteomyelitis with adjacent arthritis in experimental animals. Varying treatments have been suggested. Farr[6] and others advise early joint drainage, followed by active motion. Reich[13] cautions against opening the joint capsule and prefers drainage of the shaft of the involved bone, while Wilensky[16] teaches incision only after the abscess has ruptured through the capsule, except in the knee, where joint incision is usually found necessary.

Reports of series of cases are relatively rare in the English literature. Caldwell,[4] Inge and Liebolt[8] and Badgley and associates[1] have reported recent series. In none have the cases been limited to the acute stage of the disease. It is felt that the comparative study of series of acute cases should be of value in determining the clinical merits of varying types of treatment.

In reviewing a group of eighty personal cases of hematogenous osteomyelitis, adjacent joint involvement was found in twenty. The series is limited to successive, unselected cases of acute suppurative, hematogenous, infectious osteomyelitis, excluding the small bones of the hand, foot and mandible, which were treated surgically. Twenty-two days was the maximum duration of symptoms at the time of drainage. All cases have been followed from six months to eight years after operation. The group of twenty cases which showed joint involvement is divided on the basis of results into three groups.

Analysis by sex, age and race is shown in *Table 1*. Thirteen patients (65 per cent) were male. The youngest patient was a female, aged 9 months, the oldest a woman of 64 years. Five were between 5 and 10 years of age, and fourteen (70 per cent) were less than 15 years.

Although the annual Negro admission to this group of hospitals averages 25 per cent, only 5 per cent of this series was colored. This one case occurred in a Negro boy, aged 12 years. The infrequence of acute hematogenous osteomyelitis in the Negro has been previously noted.[14]

The hip was involved in eleven cases, the knee in six. The ankle, sacro-iliac and elbow were each involved in one instance (*Table 2*).

Six patients had major complications on admission, excluding septicemia. The patients in this group were either seriously ill or the under-

Table 1

RESULTS IN TWENTY CASES OF OSTEOMYELITIS WITH JOINT INVOLVEMENT

	I Good (12 Cases)	II Poor (4 Cases)	III Deaths (4 Cases)	Total (20 Cases)
(1) Sex	M—8 F—4	M—2 F—2	M—3 F—1	M—13 F— 7
(2) Age	9 mos.- 43 years	11 yrs.- 64 years	9 mos.- 47 years	9 mos.- 64 years
Under 2 years	2	....	1	3
2- 5 years	2	....	1	3
5-10 years	4	....	1	5
10-15 years	2	1	....	3
15-20 years	1	....	....	1
20-25 years	....	....	....	....
25-30 years	....	....	....	....
30-35 years	....	1	....	1
35-40 years	....	1	....	1
40-45 years	1	....	....	1
45-50 years	....	....	1	1
50-55 years	....	....	....	....
55-60 years	....	....	....	....
60-65 years	....	1	....	1
Average	10.1 yrs.	36.2 yrs.	14.4 yrs.	16.1 yrs.
(3) Race	W—11 C— 1	W—4	W—4	W—19 C— 1

Table 2

SITE OF INFECTION, COMPLICATIONS AND DURATION OF SYMPTOMS

	I Good (12 Cases)	II Poor (4 Cases)	III Deaths (4 Cases)	Total (20 Cases)
(4) Joint Involved and Bone of Origin				
Hip, femur	4	---	1	5
Hip, acetabulum	3	1	---	4
"Hip" (site undetermined, early death)	---	---	2	2
Knee, femur	2	1	---	3
Knee, tibia	1	1	1	3
Elbow, ulna	1	---	---	1
Ankle, tibia and fibula	---	1	---	1
Sacro-iliac, ilium	1	---	---	1
(5) Other Complications on Admission				
Lobar pneumonia (unresolved)	---	1	1	2
Lobar pneumonia (unresolved) and otitis media	1	---	---	1
Otitis media and pathologic dislocation involved hip	1	---	---	1
Draining mastoid wound (operation 3 days previous)	1	---	---	1
Separation distal femoral epiphysis (involved knee)	---	1	---	1
(6) Duration of Symptoms at Time of Operation				
Under 48 hours	1	---	1	2
2- 4 days	4	1	1	6
5- 7 days	4	---	---	4
8-10 days	---	---	---	---
11-13 days	---	1	---	1
14-16 days	---	---	2	2
17-19 days	1*	1	---	2
20-22 days	2**	1	---	3
Average	8.2 days	14 days	9.7 days	9.6 days

*1 knee from femur in female aged 15 months.

**1 hip from femur in female aged 10 mos. 1 sacro-iliac from ilium in male aged 15 years.

lying bone lesion was advanced, or both conditions were present. In one of the patients with unresolved lobar pneumonia, the pulmonary findings were so atypical that he had been previously transferred from the general hospital to the tuberculosis sanitarium with the diagnosis of pulmonary tuberculosis. In the girl with separation and displacement of the distal femoral epiphysis the duration of the symptoms on admission was nineteen days, while in the infant with pathologic dislocation of the involved hip the symptoms were of twenty-two days' duration.

The duration of symptoms prior to drainage in Group II was nearly double that of Group I. In the latter group, drainage was performed on nine occasions within one week following the onset. In the remaining three cases, two of the patients were aged 10 and 15 months, respectively, and in the third the sacro-iliac joint was involved. It has been shown by Green[7] that this disease exhibits vastly different characteristics in infancy from those in subsequent years.

Diagnosis is usually difficult, particularly in the early stages of the disease, at which time the joint symptoms are usually predominant and adjacent bone symptoms are obscure. Differentiation between tuberculosis, acute non-suppurative synovitis and traumatic lesions is usually essential. The history, physical examination, indicated laboratory examinations and roentgenograms should all be carefully analyzed. The most valuable single diagnostic procedure is aspiration, particularly when the hip joint is involved. When turbid fluid showing pus and bacteria on smear and culture, or when gross pus is obtained it is felt that joint drainage is indicated regardless of the site of origin of the infection. Roentgenograms will remain negative until after extensive bone damage has oc-

curred. Final diagnosis of the site of underlying bone disease is usually made from roentgenograms sometime subsequent to drainage.

Only cases in which pus, gross or microsopic, was obtained on aspiration, and subsequent x-ray examination revealed destructive bone changes adjacent to the epiphyseal line or joint, are here considered to be suppurative arthritis resulting from adjacent osteomyelitis.

Classed as immediate drainage are all joint evacuations performed within eight hours of admission. Thirteen cases were so treated (*Table 3*). Preoperative observation was employed when the diagnosis was in doubt, or when the patient's general condition was felt to contraindicate immediate joint drainage.

The type of local treatment employed varied considerably with the pathology found. No joint was incised without preliminary aspiration, and if doubt regarding the character of the exudate still existed, pre-incision culture was made. When the general condition was felt to contraindicate incision drainage, repeated aspiration was done. In the case of a male, aged 15 months, with lobar pneumonia, acute otitis media and involvement of the knee from the femur, aspiration was repeated at three-day intervals until the general condition was considered suitable for incision drainage on the twenty-first hospital day. In five additional cases the same principle was employed over a shorter time, for similar reasons. The principle of early, free, continuous drainage is considered basic, and incision is felt to accomplish these ends more thoroughly than is aspiration. Within the past three years repeated attempts have been made to substitute aspiration for incision drainage. This procedure has proven valuable in acute, hematogenous, suppurative synovitis, but was successful in only one instance in this series. Joint aspiration was combined with drainage of adjacent subcortical abscess in the case of a white male, aged 7 years,

Fig. 1

Female, aged two years. Four months after incision drainage of hip. Symptoms at operation of sixty-four hours duration. Site of infection, ilium. Streptococcus non-hemolyticus recovered from blood and wound. Wound healing time, two months. Roof of acetabulum irregular. (Group 1).

Table 3

TREATMENT

	I Good (12 Cases)	II Poor (4 Cases)	III Deaths (4 Cases)	Total (20 Cases)
(7) Treatment (initial local)				
Time				
Immediate drainage following admission	7	3	3	13
Preoperative observation (8 hours—15 days)	5	1	1	7
Type				
Joint incised and drained	6	—	2	8
Joint aspirated; subsequent incision and drainage (8 hours—21 days)	4	—	1	5
Joint and adjacent soft tissue abscess incised and drained	—	2	1	3
Joint aspirated and adjacent subcortical abscess incised and drained	1	—	—	1
Joint aspirated (repeatedly)	1	—	—	1
Joint and adjacent subperiosteal and subcortical abscess drained	—	1	—	1
Soft tissue abscess incised and drained	—	1	—	1

with involvement of the knee from the tibia. The local symptoms were of three days' duration. Turbid fluid containing pus cells was aspirated from the knee. The tibia was drilled and cortical window removed. *Staphylococcus albus* was recovered from the tibia. Blood and joint cultures showed no growth. No additional joint drainage was employed, as the joint symptoms rapidly subsided. It is felt that surgical release of interosseous pressure within the tibia prevented further drainage into the knee joint. Vaseline pack drains were used in all cases of incision drainage, both in the joint and in adjacent incisions when present.

Phemister[12] feels that intra-articular pressure increases cartilage destruction in pyogenic arthritis, and advises the use of traction as an aid in reducing this pressure. In this series postoperative traction was used in ten of the eleven cases of hip involvement. In the additional case (Group I) a spica cast was employed.

In the six cases with knee involvement traction was not employed. A pressure dressing of the "muff" type was used in one case, while in the remaining five a cast was employed because of adjacent pathology. Casts were also used for postoperative immobilization of the elbow and ankle. Where casts were employed, the Orr principles of rest and infrequent dressings were followed.

In one case (hip) a convalescent brace was used after removal of a spica cast.

In thirteen (65 per cent) cases suppurative arthritis was the only pathologic condition found on initial drainage (*Table 4*). Joints involved were: hip, nine; knee, two; elbow, one; and sacro-iliac, one. Within this group preoperative roentgenograms were considered negative except in the sacro-iliac. The joint symptoms were predominant and preoperative diagnosis of osteomyelitis could be definitely made only in this one case. Exact diagnosis of the initial bone lesion was made from subsequent roentgenograms. Included is a white male, aged 43 years, whose hip joint was apparently involved from activation of a low-grade lesion of Brodie's type within the femoral head by a fall onto the hip forty-eight hours prior to onset of the acute symptoms. No

Table 4

PATHOLOGY AND BACTERIOLOGY

	I Good (12 Cases)	II Poor (4 Cases)	III Deaths (4 Cases)	Total (20 Cases)
(8) Pathology Found at Operation				
Suppurative arthritis	10	—	3	13
Suppurative arthritis; adjacent subperiosteal and/or subcortical abscess	1	1	1	3
Suppurative arthritis; adjacent soft tissue abscess of bone origin	—	1	—	1
Suppurative arthritis with pathologic dislocation of joint and soft tissue abscess	1	—	—	1
Suppurative arthritis with epiphyseal separation and adjacent soft tissue abscess of bone origin	—	1	—	1
Suppurative arthritis; capsule ruptured with soft tissue abscess	—	1	—	1

(9) Bacteriology	BL	WD	BL	WD	BL	WD	BL	WD
No growth	8	6	1	1	2	—	11	7
Not of record	2	—	2	—	—	—	4	—
"Staphylococcus"	—	1	—	1	—	—	—	2
Staphylococcus albus	—	1	1	1	1	1	2	3
Staphylococcus aureus	—	—	—	—	—	1	—	1
Streptococcus hemolyticus	1	2	—	—	—	—	1	2
Streptococcus non-hemolyticus	1	2	—	—	—	—	1	2
Pneumococcus	—	—	—	1	—	1	—	2
Bacillus pyocyaneus	—	—	—	—	—	1*	—	1
Streptococcus hemolyticus and *Staphylococcus aureus*	—	—	—	—	1	—	1	—

*and spinal fluid.

history of previous hip symptoms could be obtained.

In three cases (15 per cent) adjacent subperiosteal and/or subcortical abscesses were found. The knee was involved in two cases, the ankle in one. The ankle involvement (Group II) occurred in a female, aged 64 years, and apparently arose from activation of immediately adjacent low-grade lesions of the Brodie's type within the tibia and the fibula, following injury to the ankle in a motor accident three months previously. Mild symptoms dated from the day of accident. The acute symptoms were of three days' duration at time of operation. Within this small group clinical diagnosis of the underlying osteomyelitis was easily made, and in one case (knee, Group III) with symptoms of fourteen days' duration, preoperative roentgen diagnosis was obvious.

Fig. 2

Male, aged thirty-nine years. Four months after incision drainage of soft tissue abscess of hip of joint origin. Symptoms at operation of twenty-one days duration. Site of primary infection, ilium. Pneumococcus recovered from wound. Wound healing time, three and one-half months. Destructive changes in femoral head and acetabulum. (Group 2).

In the remaining four cases (20 per cent) the acute, local symptoms were of thirteen to twenty-two days' duration and averaged 18.7 days. The soft tissue abscess present in each case was suggestive of osteomyelitis and preoperative roentgenograms revealed the site of origin. The only good result obtained in this group was in a female, aged 10 months, with involvement of the hip from the femoral neck.

In seven cases (35 per cent) culture from the joint and blood showed no growth. In one of these (knee, Group I) with symptoms of three days' duration, a subcortical abscess in the adjacent tibia was drained, from which a *Staphyl-*

Table 5

HEALING TIME AND JOINT FUNCTION

	I Good (12 Cases)	II Poor (4 Cases)	III Deaths (4 Cases)	Total (20 Cases)
(10) Wound Healing Time*	2 wks.-4 mos.	3.5 mos.-3 yrs.		2 wks.-3 yrs.
Two weeks to 1 month	4	...	...	4
One to two months	4	...	...	4
Two to four months	3	1	...	4
Two years	...	1	...	1
Three years	...	1	...	1
Average	1.8 mos.	21.1 mos.		5.9 mos.
*One case aspiration only, Group I. One case amputation 8 months after drainage, Group II.				
(11) Results				
Joint painless and stable, range of motion not less than 75 per cent in all directions (hip 7, knee 3, elbow 1, sacro-iliac 1)	12	...	...	12
Joint ankylosed, excellent functional result (ankle)	...	1	...	1
Joint stable, not entirely painless on weight bearing and/or motion less than 50 per cent in one or more directions (hip 1 knee 1)	...	2	...	2
Joint painful and unstable, requiring amputation (knee)	...	1	...	1
Died (hip 3, knee 1)			4	4

ococcus albus was obtained on culture. In this group the average duration of symptoms prior to drainage was 6.8 days.

In thirteen cases (65 per cent) a positive joint culture was obtained, and in five of these a positive blood culture was also present. In an additional case spinal fluid culture was positive, although no growth was obtained from the blood. In this group the average duration of symptoms prior to drainage was 11.3 days. It is considered significant that of the six cases in which a staphylococcus was cultured from the joint only two were in Group I, while all four cases in which a streptococcus was isolated fell within this group.

Fig. 3-a

Fig. 3-b

Male, aged fifteen years. Symptoms at operation (drainage sacro-iliac joint) of twenty days duration. Site of infection, ilium. *Staphylococcus albus* recovered from wound. Wound healing time, four months. (Group 1).
(a) Nineteen days after onset. Erosion of ilium adjacent to sacro-iliac joint.
(b) Four months after drainage. Iliac erosion decreased. Proliferative changes this area. A portion of the iliac window removed at operation is visible.

Table 6

DEATHS

	I Good (12 Cases)	II Poor (4 Cases)	III Deaths (4 Cases)	Total (20 Cases)
(12) Apparent Cause of Death				
Male, aged 47 years. Persistent septicemia, *Streptococcus hemolyticus* and *Staphylococcus aureus*. Termination nine days after drainage of knee and tibia	—	—	1	1
Male, aged 8 years. Sepsis. Capital femoral epiphysis extruded 6 weeks after incision and drainage of hip. Persistent *Staphylococcus albus* septicemia with multiple deep and superficial abscesses. Termination 66 days after drainage	—	—	1	1
Male, aged 2 years. Pneumonia. Termination 15 days after incision and drainage of hip. Pneumococcus recovered from wound at operation. Blood culture, no growth	—	—	1	1
Female, aged 9 months. Meningitis. Termination 18 days after incision and drainage of hip. *B. Pyocyaneus* recovered from wound at operation and from spinal fluid. Blood culture, no growth.	—	—	1	1

Wound healing time was arbitrarily chosen as the time required for final healing of all wounds, with separation of the crust and complete epithelialization (*Table 5*). In one case (Group II, healing time three years) sequestrectomy was required before wound healing occurred.

It is impossible to state that any given case of osteomyelitis has reached "final" arrest, and it is fully realized that regrouping may be necessary at some future date.

Results are classed as good or poor on the basis of active functional use and joint motion, as shown in *Table 5*. While the sacro-iliac cannot be grouped by range of motion it met the other qualifications of Group I and is included therein. Also included is a female, aged 10 months, with local symptoms of twenty-one days on admission: osteomyelitis of the neck of the femur with pathologic dislocation of the hip and a periarticular soft tissue abscess. Incision was made and drainage established after twenty-four hours' traction. Culture of blood and wound showed no growth. Wound healing time was twenty-two days. The hip remained unreduced after traction and subsequent closed manipulation. Open reduction and shelf operation was done two years following drainage without exacerbation in the subsequent two and one-half years' observation.

Fig. 4-a

The only amputation was in a male, aged 31 years, a farmer with local symptoms of thirteen days' duration on admission. He had osteomyelitis of the proximal end of the tibia with soft tissue abscess of the leg and knee involvement. Immediate incision was made with drainage of joint and soft tissue abscess. Culture of blood gave no growth; of knee and soft tissue abscess, "staphylococcus."

Sequestration (clinical or roentgenographic) occurred in only one case, which is included in Group II because of limited knee joint motion. A girl of eleven years had local symptoms of nineteen days' duration on admission, osteomyelitis of the distal end of the femur with soft tissue abscess of the thigh, separation and displacement of distal femoral epiphysis, and knee joint involvement. Immediate incision was made with drainage of joint and soft tissue abscess. Culture of blood, joint and abscess gave *Staphylococcus albus*. Subsequent sequestrectomy was done of the distal end of the femoral shaft. Wound healing time was three years.

Fig. 4-b

Male, aged fourteen years. Symptoms at operation of eight days duration. Site of infection, olecranon. No growth, blood or wound. Wound healing time, two and one-half months (Group 1).

(a) Thirteen days after incision drainage of elbow. Areas of decreased density proximal end of ulna adjacent to epiphyseal line.

(b) Four and one-half months after drainage. The proximal end of the ulna appears normal except for premature closure of epiphyseal line.

No pathologic fracture, epiphyseal separation or dislocation occurred in this group during treatment.

Deaths in the series totaled four, a mortality rate of 20 per cent (*Table 6*). In two cases blood culture was repeatedly positive with duration of local symptoms prior to surgical drainage of four and fourteen days, respectively.

One death resulted from lobar pneumonia fifteen days following surgical drainage. The joint symptoms developed two weeks following a previous attack of "pneumonia," type unknown, and were of fourteen days' duration at the time of drainage.

One death occurred from *Bacillus pyocyaneus* meningitis eighteen days following surgical drainage. The local symptoms were of seven days' duration on admission. Because of acute bronchitis the joint was aspirated at three-day intervals and surgical drainage deferred until the sixteenth hospital day.

No intravenous medication other than repeated blood transfusion was given any patient in this group.

DISCUSSION

It is considered significant that in twenty successive unselected cases of this disease sequestration occurred in only one. This is not the usual experience in cases of such duration (average 9.6 days) when the joint is not involved, yet it is of common occurrence when drainage is instituted within a few days following the onset. It is felt that this is best explained by regarding involvement of the joint as a mechanical decompression of the involved bone, whereby further bone damage is diminished or prevented. A review of the varying details of treatment employed in this series indicates that the underlying bone lesion may be adequately drained by incising the joint, or that joint incision drainage may be avoided in certain cases by direct drainage of the bone lesion.

Grossly and microscopically, differentiation between sterile and non-sterile joint effusions is often impossible. When the clinical and roentgenographic course prior to and subsequent to drainage is also indistinguishable, it seems apparent that the exciting cause must be similar in both groups regardless of cultural reports. As the acute symptoms averaged 6.8 days' predrainage duration in the culturally sterile effusion group, and 11.3 days' in the culturally positive group, it is felt that joints must possess certain defense properties which enable them temporarily to resist certain infections at least, but that these properties may in time be overcome, and bacteria may then live and multiply within the joint.

CONCLUSIONS

(1) In a series of eighty cases of acute, suppurative, hematogenous, infectious osteomyelitis, adjacent suppurative arthritis was present in twenty (25 per cent) on first examination.

(2) In early diagnosis of this complication, aspiration of the involved joint is felt to be the most valuable single preoperative procedure. The x-ray is of value only after extensive bone changes have occurred.

(3) In acute, monarticular, suppurative arthritis the possibility of osteomyelitis of the adjacent bone must be considered.

(4) Joints apparently possess considerable temporary powers of resistance to infection from adjacent osteomyelitis.

(5) Adjacent joint involvement in acute osteomyelitis apparently aids in decompression of the infected bone, thereby reducing subsequent damage therein.

(6) Early incision drainage of the joint is felt to be the treatment of choice, both for the joint complication and the underlying bone lesion.

(7) The prognosis for the preservation of joint function is good when early adequate drainage is obtained.

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DISCUSSION (*Abstract*)

Dr. Robert R. Jones, Jr., Durham, N. C.—Dr. Robertson's paper has emphasized a frequent complication of acute osteomyelitis beginning at those epiphyseal lines which are largely intracapsular. Experimental data, the local pathology observed at operation, and the clinical course of these cases point to frequent joint infection secondary to primary localization in the bone. Lexer, in 1896, after injecting a broth culture of staphylococcus into the veins of rabbits, noted that the subperiosteal abscesses of infection in the neck of the humerus and the neck of the femur are worth noticing not only for their frequency, but also because they perforate into the adjacent joints. We have noticed this course of events in rabbits as have others who have been interested in the production of experimental osteomyelitis. It is a not uncommon occurrence in draining a pyarthrosis of the hip to notice that the synovial-periosteal reflection along the neck of the femur has been stripped up and perforated by pus arising from the epiphyseal line beneath. The clinical course of these patients with extensive destruction of the bone primarily involved stands in contrast to the minimal bone involvement that occurs in cases with a primary synovial infection.

Dr. Robertson has emphasized the value of aspiration of the joint as a diagnostic measure and early drainage of the joint as the treatment of choice. His argument that drainage into the joint has a decompression effect, preventing rapid extension of the infection in the bone, is very attractive and possibly in the future drainage of the joint alone which he advocates will be recognized as the treatment of choice. Certainly it deserves a trial. His results and those which have been reported in the literature point towards the necessity of early diagnosis and drainage if success is to follow this method.

Our method of handling these cases has been to expose the joint on the operating table, once the diagnosis has been made, and if aspiration is negative the metaphyseal side of the epiphysis is drilled. If aspiration yields pus the joint is drained and the bone drilled also. Should there be a large subperiosteal abscess or a soft tissue abscess connected with the joint space simple drainage of the abscess is all that is done. We have recently reviewed twenty cases of osteomyelitis of the upper end of the femur which have been seen in the past six years and our studies show that cases which are operated upon within the first ten days do much better than those in whom operation is deferred until later. Also, those cases which are treated by traction or in a cast without open drainage showed the poorest results in the group.

Dr. Randolph L. Anderson, Charleston, W. Va.—Dr. Robertson's paper is of interest first, because of the high frequency of osteomyelitis; secondly, because of the relatively high frequency of joint complications; and thirdly, because there is a rarity of statistical studies.

I can recall distinctly that it was believed by many about ten years ago that joint complications in osteomyelitis were caused usually by faulty operative technic in which the joint was accidentally penetrated while bone drainage was being established. This view, I believe, is held by few at this time, since we know that joints may now become involved either through lymphatic channels or by the breaking through of the infection from the contiguous bone into the joint. In fact, I have seen cases in which the adjacent joint was involved in which no operation had been performed.

It is generally considered now that neglect of adequate drainage in osteomyelitis may result in the infection's going eventually into a joint. It seems to me that this is certainly an argument in favor of some type of early drainage.

Dr. Robertson's percentage of joint involvements in these acute cases was 20. In Beckman's, Lewis', the Mount Sinai series and others the percentage varied from 6 to 48. However, these series were not exclusively acute cases. I have not made anything like a complete statistical study of my own cases, but in the last twenty cases seen, fourteen were chronic and joint involvement was present in five, or 35 per cent. Six were acute cases in which joint involvement occurred twice, or 33 1/3 per cent. Of these twenty cases, one was a colored boy. The incidence of 5 per cent coincides with that of Dr. Robertson's series.

I agree entirely that aspiration is the most valuable diagnostic procedure in these cases. I might suggest that in cases in which there is a question as to whether or not organisms are present in the joint fluid, an examination of the joint sugar is a rather quick method of determining whether or not micro-organisms (of the pyogenic variety) are actually present. When micro-organisms are present there is usually an absence of joint sugar and vice versa, if organisms are not present, sugar is present. This procedure may save valuable time in treatment, since it is naturally much more quickly done than a culture and it is more conclusive than a smear.

If bacteria are present, I agree with Dr. Robertson that early incision and drainage should be instituted. If they are not present, aspirations at intervals with examinations of the joint fluids should be performed.

It is my belief, however, that the primary treatment should be the treatment of the primary lesion, the osteomyelitis.

As Wilensky and others have said, in some instances the osteomyelitis and the joint infection may be coincident in time, in which event the two must be treated coincidentally. In cases in which this does not occur it does not seem to me that a differential diagnosis between osteomyelitis and a joint infection is usually difficult. In osteomyelitis there is ordinarily a very acutely tender point a little above or below the joint and, in

addition, a firm, steady pressure over the involved bone at a distance from the infection will, within a few seconds lead to exquisite pain. Also, in joint infection any movement of the joint is accompanied by exquisite pain, and muscle spasm is much more acute than in osteomyelitis.

Dr. Robertson says: "The principle of early, free, continuous drainage is considered basic and incision is felt to accomplish these ends more thoroughly than is aspiration." "Vaseline pack drains were used in all cases of incision drainage both in the joint and in adjacent incisions when present." It is not quite clear to me just how vaseline pack drains are used in the joint incisions and I should appreciate an elaboration of this point.

It is also not clear to me just what Dr. Robertson meant when he said that sequestration occurred in only one case. Does this mean that it was necessary to remove a sequestrum from the affected bone in only one case? If this is so, this is certainly a very small percentage.

Dr. Robertson says: "A review of the varying details of treatment employed in this series indicates that the underlying bone lesion may be adequately drained by incising the joint or that joint incision drainage may be avoided in certain cases by direct drainage of the bone lesion." Does this mean that there is a choice of treatment either by treating the joint or the bone lesion? Is it advocated that in certain cases the bone lesion be treated simply by treating the joint involvement? It was my impression that the best treatment of the bone and joint lesion ordinarily was to treat the bone lesion first.

Dr. Robertson (closing).—I agree with Dr. Jones and Dr. Anderson that the preferable treatment is drainage of the bone lesion rather than incision and drainage of the joint if diagnosis of the underlying osteomyelitis is made before joint involvement occurs. In all cases comprising this series, however, joint involvement had occurred at the time of my initial examination. Joint drainage alone usually provides adequate drainage of the adjacent osteomyelitis, as the bone infection has apparently been adequately decompressed by drainage into the involved joint.

I have used vaseline pack drains following joint incision in exactly the same manner as in drainage of the bone, namely, the cone-shaped pack as described by Orr. To date, this has proven satisfactory in the acute stage of the disease. It is not used in chronic, neglected cases with large, soft tissue abscesses. Here rubber tube or tissue drains have usually proven more desirable.

Sequestra were demonstrable in only one case in this series. This low incidence of sequestration is construed as an added indication that the focus within the bone had been adequately decompressed by drainage into the adjacent joint.

It is realized that no far-reaching conclusions can be drawn from the analysis of this small group of acute cases, but to me the excellent clinical results which have been obtained to date are surprising. Let me emphasize the fact that these cases were all in the acute stage of the disease, with joint involvement of proven bone origin. Hematogenous joint infection, and chronically infected joints, present problems which differ widely from the acute cases.

BILE TREE VISUALIZATION*

ITS SURGICAL IMPORTANCE

By ROBERT L. PAYNE, M.D.
Norfolk, Virginia

The object of this presentation is to bring before you the viewpoint of the general surgeon with regard to the value of a technical procedure which should be more universally employed by surgeons treating bile tract disease. Poor results in the treatment of bile tract disease are all too frequent, and if by more careful diagnostic methods complications and secondary operations can be avoided, this should be a valuable addition to our study of biliary tract lesions. While it will be my endeavor to present several types of cases representing the value to the surgeon of this method of procedure, yet the principle purpose is to emphasize the value and necessity of x-ray studies of the bile tree during operative procedures.

This procedure is erroneously considered a new thing, and it is strange to find how few general surgeons are familiar with the method. As far back as 1922, Patterson and Tenney[1] demonstrated a biliary fistula by bismuth paste injection, and since 1926, Dr. José Saralegui[2] has been using the method routinely. Numerous other men have reported on the employment of a method for visualizing the bile tree postoperatively, and in 1932, Mirrizi[3] reported a large series of cases in which he had studied the bile tree on the operating table after the common duct had been opened. In 1935, Dr. Charles G. Mixter demonstrated to me his method of x-ray visualization of the bile tree before the common duct was opened, and the details of Dr. Mixter's work were splendidly presented by Robins and Hermanson[4] in April, 1936. Since March, 1935, I have employed the Mixter-Robins-Hermanson technic in my bile tract surgery whenever it was possible.

It is necessary that the general surgeon have accessible in his x-ray department a portable machine which has sufficient capacity to make a good picture with very short exposure. The exposure should not exceed 1 second, and preferably it should be ¼ second, made with a machine having capacity up to 30 or more milliamperes. We have made our exposure in ½ second or less by stepping up our portable machine to 20 mil-

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liamperes. Respiratory movements of the patient during an operation are often rapid, and with wide excursion. It is therefore better that the patient be sufficiently anesthetized to have a quiet respiratory movement, and that the x-ray exposure, if possible, be made between the diaphragmatic excursions. It is not essential to have a curved metal tunnel under the patient's back as recommended by Dr. Hermanson, though I am sure that this facilitates the making of more than one exposure on the table during the operation.

Technic.—The method is nothing like so complicated or difficult as many men infer it to be. Before the patient is anesthetized, a large plate is placed under the liver region. After the gallbladder and common duct are thoroughly exposed, the surgeon then decides whether he can correctly interpret the pathologic condition present, or whether he needs the help of the x-ray. It is needless for me to dwell upon the importance of a large experience and an intimate knowledge of living pathology.

Bile tract surgery is not a field which a novice should enter. X-ray visualization is by no means necessary in every case, and under no circumstance is it recommended to the inexperienced operator as a routine or as a method of diagnosis when all of the other factors in the problem have not been thoroughly and carefully weighed.

Having decided that x-ray help is indicated, then the first step is to put a small clamp loosely on the cystic duct to prevent backflow of the opaque medium into the gallbladder. If the indications for cholecystectomy are clearly cut, the removal of the gallbladder is best done before the x-ray visualization is undertaken. All metal instruments, including towel clips, are temporarily removed from the operative field, and the next step is the introduction of a No. 18 gauge needle into the common duct. This needle may be a short-shouldered tonsil needle with an angle of 45 degrees to it, but one may use the ordinary, long spinal needle which bends readily in one's fingers, and can thus be made to have an angle of 45 degrees about 1 cm. from the point. This angle in the needle is important in that it provides for the point of the needle by slightly angling the syringe to lie parallel to the long axis of the common duct. If a perfectly straight needle is used, there is the possibility of piercing the portal vein, and this danger is enhanced by respiratory movements. The straight needle, after the duct is collapsed by aspiration, may be impossible to hold in the lumen of the common duct, and accordingly, the opaque medium may be deposited in the layers of the common duct, behind the duct, or even in the portal vein or hepatic artery. When the needle is properly placed in the common duct, the next important step is completely to empty all of the bile in the duct system which is sometimes small in quantity, but often, if there is an obstruction, may amount to a large quantity. After the ductal system is thoroughly aspirated, then 20 to 25 c. c. of hippuran is slowly injected through the same needle which has already been placed in the common duct for aspiration. The needle is then withdrawn; any excess of opaque medium which may have escaped around the needle puncture is carefully sponged away, the wound is covered with a sterile towel, the portable x-ray is placed in position and the exposure made. Sometimes spasm occurs at the sphincter of Oddi immediately following the injection, thus giving a false impression, in the first x-ray exposure, of obstruction at this point. If the patient's condition is satisfactory and the anesthetic smooth, it is preferable to wait between 10 and 15 minutes and then make the second exposure. When visualization of the bile tree is undertaken postoperatively through a T-tube or fistula, it is always advisable to make two or more exposures at 15-minute intervals, lest one be led astray in his interpretation by functional spasm at the sphincter of Oddi. It is always advisable on the operating table to make an exposure, after the operative work has been completed, by injecting additional opaque medium through the tube inserted in the common duct for drainage purposes.

X-ray visualization of the bile tree during the operation and before the common duct has been opened, is the most accurate method we now have for determining the anatomical and functional status of the ducts and the sphincter of Oddi.

Without x-ray at operation understanding of the condition of the bile tree and sphincter must depend, at the time of operation, on a highly intelligent interpretation of living pathology based on a wide experience and upon indirect evidence. Examples of indirect evidence are: presence of jaundice, or the history of jaundice; contracted gallbladder; dilated, thickened or bile-stained common duct; stones impacted in the cystic duct; and, small mass felt around the location of the ampulla of Vater, or induration at the head of the pancreas. There are many pitfalls in this

line of reasoning, and one must always remember that jaundice is not a symptom of cholecystitis, and therefore, cholecystectomy alone in the presence of jaundice is an incomplete operation except where acute cholecystitis is the cause of a hepatitis associated with cholangeitis. It is a known fact that jaundice is absent in the presence of common duct stone in 35 to 40 per cent of cases.

Without x-ray postoperatively, understanding of the status of the bile tree must depend on certain indirect criteria. Many surgeons postoperatively thus satisfy themselves by evidence such as the clearing of jaundice or its disappearance; stool examinations for bile; study of external drainage of bile chemically and microscopically, and by irrigations of, and by frequent clamping off of the T-tube.

With x-ray studies done at the time of operation we are furnished with visualization of the bile tree, which provides accurate information on the anatomy and functional status of both the ductal system and the sphincter of Oddi. This means the shape, contents and motor function of the ducts, as well as the physiology of the sphincter. In other words, there is the determination of the patency of the ducts and sphincter; presence of obstruction, and whether the obstruction is due to spasm at the sphincter, fibrous obstruction, or to stone. In addition, dilatation and contraction of the hepatic ducts and radicles are portrayed, and the size and presence of angulation in the common duct is demonstrated. Furthermore, at the finish of the surgeon's operative measures directed to pathologic conditions of the common duct found, the patulency of the duct and sphincter may be determined by x-ray. Thus, a stone not found, but thought to have been pushed into the duodenum, may still be demonstrated in the ampulla. This is an accurate means by which secondary operations on the common duct may be prevented.

With x-ray postoperatively, invaluable information is obtained through the aid of hippuran injections. For instance, many surgeons in acute cases prefer drainage alone, with the intention of performing a subsequent operation to deal with the pathological condition present.

By injections of hippuran one is able to determine the cause of persistent or recurring biliary fistula, with especial emphasis on the presence of internal biliary fistula. In addition, through x-ray visualization, one may reasonably assume the presence of cholangeitis, or unusual dilatation or diverticula of the main or terminal ducts. The presence of stone or stricture producing obstruction is readily outlined, and the question of neoplasm in the ducts or pancreas is brought out for consideration. One of the most important features developed by x-ray visualization is reflux of hippuran in the pancreatic duct. This is not only indicative of obstruction at the ampulla, but also indicates the probable existence of pancreatitis because of the part that reflux bile up the pancreatic duct plays in pancreatitis, which is definitely suggested by the x-ray delineation of the pancreatic duct.

Many surgeons are not using this valuable method of studying their common bile duct problems, the principle excuse being that the method materially complicates and prolongs the operative technic. They argue that all information desired can be obtained by manipulation after the common duct is opened. The fallability of surgeons in clearing up common duct obstructions at one operation is notorious. Several years ago I reviewed 600 of my operations upon the biliary tract, and found that in this series stones were found in the common duct in only 8 per cent of the total number.

I am now convinced that I left behind stones which should have been removed had x-ray visualization been practiced on these cases at the time of operation. In my later experience with the aid of x-ray visualization, I have been recovering stones in 20 per cent of my cases, and find indications for opening the common duct in one out of every four cases of surgery undertaken on the bile tract. This lesson is sufficient to indicate the necessity of more careful study of the common duct and sphincter when operating for bile tract disease, and especially to emphasize the value of x-ray visualization of the bile tree at the time of operation.

Case 1, Simpson 16055 (Fig. 1).—The preoperative diagnosis was cholecystitis with intermittent common duct obstruction; intermittent jaundice.

Operative findings, gallbladder small, atrophic; measuring 1.25 cm. in diameter and containing one stone. Common duct thin, blue, dilated to three times the normal size; no stones found in common duct; unable to pass fluids through dilating cannula into duodenum; stricture from cicatrix and spasm at ampulla.

Operation, cholecystectomy; hepatic and common duct explored; stricture at sphincter dilated to 10 mm. and T-tube inserted with short arm above and long arm down to stricture.

X-ray three weeks later through T-tube. All biliary ducts are well visualized, including the stump of the cystic duct. The hippuran empties normally from the common duct into the duodenum.

Case 2, Sawyer 16075 (Fig. 2).—The diagnosis was deep jaundice; common duct obstruction. Cholecystectomy six months previously.

Operative findings, cicatricial stricture of common duct near junction of cystic duct; no stones found; stricture incised; sphincter of Oddi dilated to 9 mm. and T-tube placed in common duct.

X-ray two weeks after operation through T-tube. All bile ducts are well visualized. There is some dilatation of the left hepatic and common bile ducts. There is complete obstruction at the ampulla, which is apparently not due to stones. This was error.

Surgeon's note: T-tube removed three weeks later, followed by hard attacks of colic, and failure of the biliary fistula to close. Operation demonstrated stone impacted in ampulla, as shown in x-ray picture.

Note at first operation: no stones were found and sphincter was dilated to 9 mm. Interpretation of x-ray study was erroneous in the first instance.

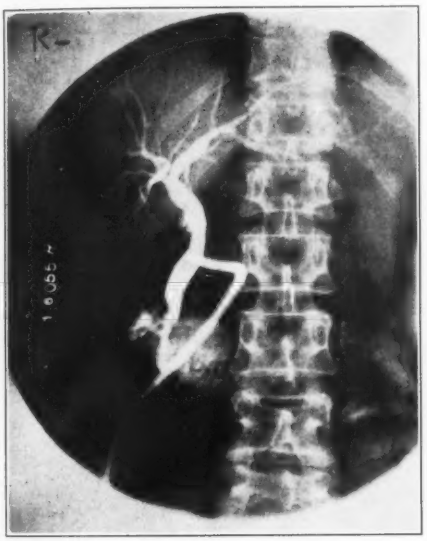

Fig. 1. Case 1 (Simpson 16055)

Case 3, Childress 16081 (Fig. 3).—The preoperative diagnosis was deep jaundice, common duct obstruction. Cholecystectomy four years previously.

The duct was dilated, thin, distended with white bile, and obstructed at the ampulla by a round tumor mass 1.5 cm. in diameter. I was unable to pass either sound or injected saline into the duodenum through the common duct.

At operation, the second portion of the duodenum was opened; specimen for biopsy was taken; T-tube was inserted in the common duct.

The diagnosis was cancer of the ampulla of Vater. Biopsy showed papillary carcinoma.

At x-ray three months later, good visualization of the biliary ducts was seen. The gallbladder was absent. There was complete obstruction of the duct at the ampulla, which is apparently not due to stones, confirming operative and laboratory diagnosis. The tube was left in for fifteen months, and later choledochoduodenostomy was done, which at this time is functioning normally.

Case 4, Carter 16041 (Fig. 4).—The preoperative diagnosis was obstructive jaundice.

At operation the gallbladder was found to be small, fibrous and atrophic. There were no stones in the gallbladder; the common duct was enormously dilated and

Fig. 2, Case 2 (Sawyer 16075)

Fig. 3, Case 3 (Childress 16081)

thinned out; the common duct was opened and a large amount of dark bile and debris was removed. It was impossible to pass a probe or inject saline solution into the duodenum. At the distal end of the common duct was a hard, irregular, nodular mass in the head of the pancreas about the size of an egg. No specimen for biopsy was taken.

Fig. 4, Case 4 (Carter 16041)

The gross diagnosis was malignancy of the head of the pancreas, obstructing the common duct.

T-tube was put into the common duct. No biopsy was done.

X-ray six months later through T-tube gave good visualization of the biliary ducts, including the small, contracted gallbladder. The hippuran emptied normally from the common duct into the duodenum; the T-tube was removed and the fistula promptly closed. The patient has remained entirely well. The pathologic condition was inflammatory rather than malignant.

Case 5, Guard 16108 (*Fig. 5*).—The preoperative diagnosis was common duct obstruction, with deep jaundice. This patient had had the gallbladder removed two years before.

At operation, the gallbladder was seen to be absent; the common duct was immensely thickened and dilated, containing three large stones, with definite stricture formation at the sphincter. The liver showed considerable hepatitis throughout the right lobe.

The common duct was opened; hepatic ducts were explored; three stones were removed from the common duct; the sphincter at the ampulla was dilated to 10 mm. and the T-tube inserted.

X-ray through T-tube eight weeks later showed the following. The T-tube is almost completely out of the common duct; only the tip remains. The common duct and stump of the cystic duct are well visualized and appear somewhat dilated. The hepatic ducts are only partially visualized. The hippuran drains through the common duct freely into the duodenum. This represents obstruction by stone and stricture, which was relieved by removing stones and dilating the stricture. Was stricture responsible for stone formation?

Case 6, Bunch 16757 (*Fig. 6*).—The preoperative diag-

Fig. 5, Case 5 (Guard 16108)

Fig. 6, Case 6 (Bunch 16757)

nosis was cholangeitis; progressive jaundice (20 to 33 mg. serum bilirubin for three months).

At operation, the gallbladder showed marked thickening of the walls, and the whole organ was deeply bile-stained. The common duct appeared thickened and bile-stained, but very slightly enlarged, if at all. There were several large inflammatory lymph nodes lying along and under the common duct. The liver was sharp-edged, but revealed considerable passive congestion; the pancreas was normal. There was no mass at the ampulla.

The gallbladder was removed and the common duct opened, and careful exploration showed no stones. The dilating cannula was passed through the ampulla of Vater. The orifice was tight, but there did not appear to be any definite stricture or spasm. X-ray of the bile tree at the time of operation gave a poor and unsatisfactory picture of the hepatic tree. The sphincter was open and hippuran passed freely into the duodenum. The pathologic condition at operation was thought to consist of general cholangeitis associated with possibly a primary hepatitis. A T-tube was placed in the common duct.

X-ray through the T-tube two months after operation. Approximately 8 c. c. of hippuran were injected, which was followed by unusual pain and discomfort. The common duct is of practically normal caliber, but shows considerable medial angulation, approximately 2.5 cm. from the ampulla. The ampulla is patulous, with some of the dye passing into the duodenum. The hepatic tree is well visualized and shows no dilatation. On the other hand, all of the ducts appear to be contracted. The liver shadow is well-defined and abnormally small and contracted. Two films were made, ten minutes apart, the second one showing rapid emptying of the ducts.

Final diagnosis was infectious cholangeitis and hepatitis.

Fig. 7-A, Case 7 (Palmer 16195)

Case 7, Palmer 16195 (Figs. 7-A, B and C).—The preoperative diagnosis was cholecystitis; subacute pancreatitis; acute obstruction of the common duct associated with deep jaundice.

At operation the gallbladder was found to be small, contracted and ruptured, with multiple stones buried in

Fig. 7-B, Case 7 (Palmer 16195)

Fig. 7-C, Case 7 (Palmer 16195)

Fig. 8, Case 8 (Morrissette 17071)

the liver substance and numerous areas of fat necrosis scattered over the peritoneum throughout the upper abdomen. The pancreas was acutely inflamed, red, indurated and covered with areas of fat necrosis. The common duct was 2.5 cm. in diameter; no stones were found, but it was definitely obstructed by stricture at the ampulla.

Cholecystectomy was done. Stricture of the common duct at the ampulla was demonstrated by x-ray; the common duct was opened and explored; no stones were found; stricture at the ampulla was dilated to 10 mm. and T-tube inserted in the common duct. The condition was x-rayed again with hippuran through the T-tube.

X-ray was made before the common duct was opened. Bile was withdrawn from the common duct with a needle and 20 c. c. of hippuran were injected into the duct. Medially the common duct showed almost acute angulation and obstruction at the ampulla. The hepatic tree showed considerable dilatation; no shadow indicating stone was seen.

X-ray was repeated through the T-tube during operation, but after dilatation of the sphincter. No dye was seen in the duodenum, indicating that the obstruction still exists and is now due to spasm. The bile ducts show practically the same amount of dilatation.

X-ray was repeated through the T-tube sixteen days later. Twenty c. c. of hippuran were injected through the T-tube; the obstruction at the ampulla has been relieved and the hippuran is emptying normally into the duodenum. The same amount of dilatation of the bile ducts was present, and the distal end of the common duct showed practically the same angulation. Valuable information was thus secured if future trouble develops.

Case 8, Morrissette 17071 (Fig. 8).—The preoperative diagnosis was cholecystitis with stones, associated with mild jaundice and probable common duct obstruction.

Operative findings were: gallbladder elongated, thickened, distended and containing many stones; the gallbladder was bile-stained; the common duct was bile-stained and dilated to 1.5 cm. with walls that were very thin.

Operation consisted of cholecystectomy. The common duct was aspirated and about 10 c. c. of dark, grumous fluid were removed. Through the aspiration needle 25 c. c. of hippuran were slowly injected into the common duct and immediately a flat x-ray plate was made. This showed dilatation of the common and hepatic ducts with obstruction at the sphincter of Oddi. No hippuran was seen passing into the duodenum. One-half cm. above the sphincter of Oddi are to be noted two round areas of lessened density, indicating the presence of two stones. The common duct was opened and two stones were removed from the ampulla of Vater, the sphincter was dilated with graduated dilators, and a T-tube inserted in the common duct. The T-tube was left in for five weeks, at which time microscopic studies and chemical analysis for chlorides and bile salts showed the bile to be normal. At this time the T-tube was removed and the patient has remained free of symptoms.

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DISCUSSION (*Abstract*)

Dr. Arthur M. Shipley, Baltimore, Md.—The mortality and morbidity of biliary duct surgery are disturbing and many patients come to second and third operations for a number of reasons. Defective biliary drainage with an ascending liver infection is a common condition. Overlooked stones in the ducts at the time of operation cause surgeon and patient trouble enough. Pancreatitis may enter the picture and stricture at the outlet into the duodenum may be present. Anatomical variation in the biliary drainage apparatus or in its blood supply is a source of worry.

Now when all of these structures are deeply placed in a fat person with a high liver and when these difficulties are increased by edema, inflammation and adhesions, it is easy to understand that any procedure that helps out in the solution of these problems is a welcome addition to our armamentarium.

There are many operative and postoperative anxieties in dealing with pathologic changes in the biliary ducts and gallbladder. Control of leakage of bile from the raw surface of the liver, secure closure of the cystic duct, avoidance of injury to the hepatic and common ducts and ligation of the cystic vessels are essential in cholecystectomy.

But these problems are relatively easy and simple when compared with the choice of procedure thrust upon the operator when dealing with a doubtful condition of the ducts.

By the very nature of things their position is a chief obstacle in estimating the pathology that is present. A part of this duct system is placed high up under the

liver, a part is found in the lateral margin of the hepatoduodenal ligament, another section behind the duodenum, a further portion surrounded by or grooving the head of the pancreas, another part joining with the pancreatic duct to form the diverticulum of Vater and a terminal portion where it passes through the sphincter surrounding the opening into the duodenum.

There is ample reason, therefore, that the literature of biliary duct surgery is voluminous and the subject matter a part of the program of every surgical congress.

There are two things that are of the utmost importance in the surgery of the hepatic and common ducts: ample drainage of bile from the liver and avoidance of losing too much bile for too long a period through an external biliary fistula. These two conditions bring about entirely different clinical and pathological pictures.

Everyone is familiar with the damaged liver due to ascending infection and poor drainage, granular and discolored, bile stained, with smooth rounded edges, often with a thickened capsule, swollen and firm. After improvement in bile drainage, if for any reason a later operation is done, one can scarcely realize that the liver is the same, so nearly does it approach the normal in appearance, in size and in consistency.

Then, who has not seen the apathetic patient, without appetite, with subnormal temperature and falling blood pressure turn his face to the wall and refuse to make a fight for life when there is a large external biliary fistula?

Therefore, the surgeon is on the horns of a dilemma. If he overlooks obstruction in the ducts and does not drain above the obstruction, the patient will go on with increasing evidences of liver damage, and when it is remembered that the physiologists can demonstrate eleven separate functions of the liver, one realizes anew how important this organ is. If he does drain and does not remove the obstruction, a permanent external biliary fistula leaves a host of evils in its wake.

I am, therefore, in hearty accord with Dr. Payne in the use of biliary tree visualization and I believe also that graduated dilators on a flexible staff have a place in the surgeon's equipment, but I feel bound to sound a warning note. Too much pressure of the injected fluid and too rough handling of the dilators has and may lacerate the common duct, especially in that portion adjacent to the opening into the duodenum and such a mishap creates a triple threat: leakage of pancreatic juice, leakage of bile and injury to blood vessels, any one, any two or all three.

Dr. Frank S. Lynn, Baltimore, Md.—Some years ago a prominent surgeon of this city and a former teacher of mine made the statement to me that an appendectomy could be one of the simplest operations in surgery, or on the other hand it might be one of the most difficult. Since that time I have often felt that the same observation might be applied to surgery of the biliary tract, and no less a person than Lord Moynihan once said that an operation on a high gallbladder was the most difficult of operations and that the removal of a Gasserian ganglion in comparison with it was work for a novice.

I am not prepared to go so far as Lord Moynihan, but I have sometimes felt that way about it. All of us are in accord with the idea that any procedure which will make our diagnoses more definite and which will contribute to the simplification of our operative procedures is received with much satisfaction. Dr. Payne has directed our attention to a procedure which I think will bring about these desired conditions in surgery of the biliary tract, and while I have had no personal experience in carrying out this technic, I think after listening to the excellent paper of Dr. Payne, it is worthy of our consideration and trial.

MANAGEMENT OF ATONIC BLADDER DUE TO OBSTRUCTION OF VESICAL NECK*

By Louis M. Orr II, M.D.
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Medical periodicals of the past decade contain a large amount of material devoted to the atonic, or so-called cord bladder, but a fairly extensive search of the literature reveals but little information on atonic bladder due to obstruction at the vesical neck.

While it is the purpose here to discuss the management of the atonic bladder which follows long-standing vesical neck obstruction as commonly found in patients with prostatic enlargement, a clearer understanding of the subject is made possible by reviewing the anatomical development of the bladder.

The gross structure of the bladder as related to bladder atony involves the rather complex muscular arrangement of the bladder walls and outlet and the equally complex system of innervation.

In embryonic life, according to Keibal and Mall, the mesenchyme is condensed and later transformed into the musculature. The first muscular layer is seen to develop as a longitudinal layer and extends from the apex of the bladder almost to the ureteral openings. The next layer to develop is the circular layer which makes its appearance at the bladder apex. Lastly, a third layer of musculature in the form of an inner longitudinal layer is formed and both longitudinal layers give off oblique bundles to the intervening circular layer.

It is thus seen how cellules and diverticula will naturally form in these weaker areas which lie in between the oblique bundles. The nerve supply of the bladder musculature is derived from two different pathways, the vesical craniosacral pathway and the vesical thorico-lum-

*Read in Section on Urology, Southern Medical Association, Thirtieth Annual Meeting, Baltimore, Maryland, November 17-20, 1936.

bar pathway, each of which is antagonistic toward the other. The craniosacral pathway consists of pre- and postganglionic cells which originate in the sacral portion of the cord and pass by way of the second and third sacral nerves to the pelvic plexus and then to the plexus located on the walls of the bladder. These nerves excite contraction of the vesical musculature exclusive of the internal sphincter and the trigonal area which it inhibits to produce urination.

The vesical thorico-lumbar pathway likewise contains pre- and postganglionic neurons which send fibers to the inferior mesenteric ganglion through the hypogastric plexus to the musculature of the bladder. The function of this pathway is to excite contraction of the trigonal area of the bladder musculature and cause retention of urine. It is therefore seen that atony of the bladder caused by disturbed innervation may involve either one or both of the above systems of innervation and thus produce different types of atony of neurogenic origin.

Although atony of the bladder is always produced by some extravesical cause and is never primary, Braasch and Thompson have recently, for the purpose of clinical convenience only, classified all types of bladder atony as being of either primary or secondary origin. The so-called cord bladder, where there is partial or complete interference with the innervation of the detrusor muscles and of all other muscular elements forming a part of the contractile mechanism of the bladder wall, is classified as being primary in origin. All other types of bladder atony resulting from interference to the outflow of urine through the vesical neck, whether it be caused by sphincteric dysfunction due to cicatricial changes in the sphincter itself, or by the obstructing prostate, are classified as secondary. It is likewise possible to have both types of atony present in the same bladder. The diagnosis of vesical atony of neurogenic origin is not difficult when the cystoscopic picture is of a greatly increased bladder capacity with the mucosa rather pale and quite smooth, beneath which are visualized the very fine, almost thread-like bands of trabeculated muscle. The cystogram (*Fig. 1*) shows a large ovoid bladder quite regular in outline and entirely without evidence of the gross trabeculation often seen in cases of prostatic obstruction. The curve of the cystometrogram is quite typical and shows definite absence of tone of the detrusor muscles. With this type of bladder there is usually pronounced clinical evidence of some neurological lesion.

The type of atony following long-standing vesical neck obstruction which is commonly caused by an hypertrophied prostate gives quite different objective findings. The bladder walls are seen to be everywhere irregular with large bundles of hypertrophied muscle interlaced throughout the walls between which are seen cellules and quite commonly diverticulous openings. The cystogram shows great irregularity of the bladder walls with oftentimes great distortion in shape due to diverticula. The curve of the cystometrogram shows evidences of muscular hypotonicity and in most instances is a fairly reliable means of ascertaining the amount of muscular reserve remaining in the walls.

The type of atonic bladder discussed by Braasch and Thompson has the same smooth outline which characterizes the atonic bladder of neurogenic origin, in which have been shown definite cicatricial changes in the internal sphincter muscles as a probable cause of obstruction. Removal of a sufficient amount of this tissue by use of a direct vision punch resulted in complete recession of residual urine in 20 of their 24 reported cases, and in the other 4, while re-

Fig. 1
Cystogram of typical atonic bladder of neurogenic origin.

tention was overcome, normal function was not completely restored.

Although one cannot help being greatly impressed by the successful results in this series, and for the description of possibly another unclassified type of atony, it seems entirely logical to raise the question of whether or not the cicatrix found involving the vesical sphincter was the uncomplicated cause of the retention of urine. The reason for this question lies in the description of the type of bladder wall found by cystoscopy and the cystogram. If such a smooth walled bladder did result from a pure vesical neck obstruction, it is quite contrary to the mechanics of the production of trabeculation by muscle bundle hypertrophy, which usually follows this type of obstruction. If this type of bladder atony were solely the result of the fibrous tissue changes found in the sphincter, it would be only reasonable to assume that the detrusor muscles of the bladder wall would follow the usual sequence of changes, that is, hypertrophy of the individual muscle bundles leading to trabeculation of the gross type, and later to loss of tone and atony from muscular decompensation that is found in all cases of pure bladder neck obstruction.

The still more remarkable feature of these cases was that the bladders regained their tonus and each patient was able completely to empty his bladder after resection of the contracted sphincters. From what knowledge has been gained in the past regarding the physiology of the bladder, these cases represent certainly many features which would seem paradoxical.

Kretschmer and Heckel, in 1932, described an interesting case of bladder atony in a male, aged 77, who had no marked urinary symptoms, but who had a urinary retention with the bladder extending upward to a point between the umbilicus and the xyphoid process. After a thorough physical examination no evidence of a neurological lesion could be found and at cystoscopy a rather moderate sized median bar was noted which was thought to be the cause of obstruction. The bladder walls showed evidence of long-standing obstruction in the form of gross trabeculation and cellule formation. At operation the median bar was completely resected and the internal vesical orifice appeared quite relaxed and sufficiently ample in size to allow the bladder to empty. Following the operation the patient was never able to urinate despite the removal of all apparent obstructing tissue, and finally died of an intercurrent disease several months later. At autopsy no demonstrable cause for the retention of urine could be found in the urinary tract.

Kretschmer advanced the very tenable theories that the cause of the bladder atony was perhaps either (1) a complete loss of muscular tone of the bladder walls due to the long years of obstruction or (2) some lesion of the nervous system involving possibly only the peripheral nerve fibers. Mention was also made of the possibility of the involvement of the muscle bundles in some form of arteriosclerosis or some type of infection localized in the bundles which was followed by the production of scar tissue which prevented sufficient contractility to overcome the retention.

Although atonic bladder due to vesical neck obstruction occurs far more frequently in the male than in the female, the occasional occurrence in the female is of more than ordinary clinical interest. The female bladder, for practical purposes, has only one sphincter muscle and obstruction to the outflow of urine occurs only after a hyperplasia or hypertrophy of the sphincter or following infection in the nature of a contracture of the bladder neck. There may be true hypertrophy of the sphincter muscle in the female. In one of our patients there was complete retention of urine from this cause and diverticula (*Fig. 2*) gave evidence of the amount of resistance offered by the vesical outlet to the contractile mechanism of the bladder. It was necessary to remove three rather deep bites of tissue from the sphincter with a Caulk's cautery punch, which was later followed by excision of the diverticula before the patient regained a normal bladder function.

Another patient had an atonic bladder which began as a purely neurogenic atony resulting

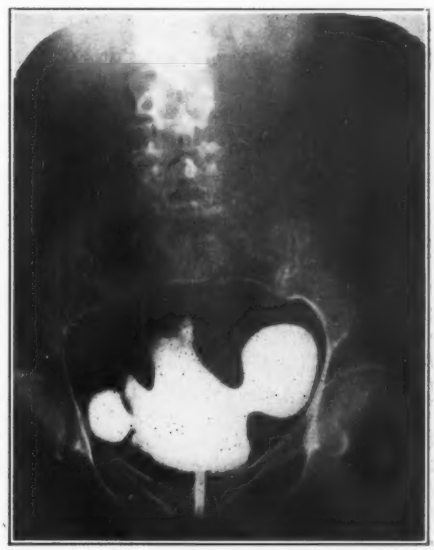


Fig. 2

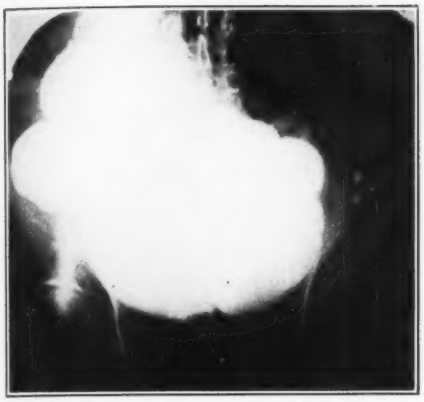
Diverticula in bladder of female resulting from vesical neck obstruction caused by cicatricial changes in the sphincter muscle.

Fig. 3
Cystogram of neurogenic bladder caused by spinal cord injury showing incompetency of ureterovesical valves allowing reflux of media into ureters and kidneys (taken in 1933).

from a compression fracture of the lumbar spine. The injury was incurred in France during the World War and an effort was at first made to establish automatic urination by overflow, but infection intervened and as a result a cystogram made in 1933 (*Fig. 3*) shows evidences of an atony of the obstructive type with marked irregularity of the vesical contour, associated incompetency of the uretero-vesical valves resulting in marked ureterectasis and pyelectasis. During the next three years very careful attention was given the urinary infection, together with frequent catheterizations and as a result a cystogram made this year (*Fig. 4*) shows sufficient recovery in the tone of the valvular mechanism to prevent reflux up the ureters. Both of these cystograms were made with the same amount of pressure as recorded on the manometer.

The treatment of the so-called cord bladder is not to be discussed at this time, as its treatment is usually secondary to that directed at the primary lesion. The loss of tone of bladders caused by vesical neck obstruction lies directly in the hands of the urologist. In all atonic bladders of this type consideration must be given first to removal of the cause of the obstruction, and secondly to proper treatment of the bladder during its period of recompensation. In the large majority of instances the dilated, insensitive bladder with residual urine of great quantity caused by the obstructing prostate will usually, sooner or later, regain its tone and be able completely to evacuate its contents. It is often necessary to watch these bladders carefully and if they do not completely empty themselves intermittent catheterization or an indwelling urethral catheter may be necessary. As time goes on it is usually found that the residual urine becomes less, the force of the urinary stream greater, together with less straining effort on the part of the patient. There are some bladders, however, which are not able to empty themselves despite the removal of the obstruction and when this persists over a period of months without improvement it is safe to presume a diagnosis of bladder atony of the myogenic type. The musculature in these cases has hypertrophied to the maximum extent and undergoes complete loss of all of its contractile powers. It is only reasonable to assume that a degree of fibrosis takes place between the muscular fibers, as the majority of these cases show infection of some degree. Between these muscle bundles cellules

Fig. 4
Same bladder as Fig. 3 after three years of treatment. No reflux noted.



No. 5
Atonic bladder of myogenic origin. Capacity over 3,000 c. c. before operation.

and diverticula are found which permit increased bladder expansion by a process of repeated stretching, but which are entirely lacking in any elasticity. As the process advances the muscle bundles become more differentiated and even if they could at this time regain their full expulsive power the contents of the bladder could not be emptied because of the large part of the bladder wall area occupied by completely atonic cellules and diverticula.

It has recently been my experience to encounter this type of bladder and the treatment, after removal of the obstruction, although at first appearing somewhat radical seems to be quite rational after an examination of the end result obtained.

A white American male, aged 68, first consulted his family physician because of an abdominal swelling and an attendant complaint of constipation. His entire urinary history consisted of an increased slowing of the stream over a period of ten years with an associated nocturia of 3 to 4 times. There was no dysuria of any marked degree. The prostate was said to be within normal limits. After a roentgenographic examination of the gastro-intestinal tract failed to reveal a cause for the swelling in the abdomen a catheter was introduced and as a result over 3,000 c. c. of clear, rather pale urine was obtained. The patient was then placed under my care and a cystogram (*Fig. 5*) was made. This shows the tremendous amount of bladder irregularity produced by the obstruction. A cystoscopy revealed a large median lobe with practically no lateral lobe hypertrophy. Laboratory studies showed evidences of moderate renal impairment, but in other respects the patient was in good condition. A prostatic resection was performed and 27 grams of tissue, representing principally the median lobe, were removed. After twenty-four hours the catheter was removed and only about two ounces of urine could be passed and this only in the sitting position. After several weeks of very careful attention to the bladder by repeated catheterizations plus the use of the indwelling catheter, the patient still was unable to pass any sizable amount of urine. Cystoscopic examinations showed an adequate opening through the prostatic urethra. Realizing that the condition was possibly one of complete muscular atony in view of the fact that no neurological symptoms were present, a permanent suprapubic cystostomy was decided upon. Upon opening the bladder the impression was at once gained that the entire outer or upper one-half of the bladder was by far more thin and atonic in appearance than the region immediately around the vesical neck. Consequently a large eliptical incision was made and a large part of the bladder resected. Three months after operation the size of the bladder (*Fig. 6*) was shown to be greatly decreased after the excision of most of the upper half. Rather than leave the suprapubic tube in permanently it was removed after four days and an indwelling catheter inserted. In one month's time the suprapubic incision was healed and the catheter was removed, but the patient was unable to urinate in the prone position. However, upon standing he was able to urinate a stream of fair force and after two weeks' time the residual urine amounted to only two ounces, which has persisted, but has not been a source of any annoyance.

It is my feeling that the result obtained was quite possibly due to the fact that by resecting a portion of the bladder wall which contained the most weakened portion the resulting bladder of diminished capacity contained musculature of sufficient contractile power to expel the urine.

Although this is but a single instance of relief by this type of treatment it is possibly of sufficient merit to

Fig. 6
Same bladder as Fig. 5 after radical excision of upper one-half of bladder and prostatic resection.

warrant further study of the musculature of the bladder in relation to the mechanism of atony, as it involves the various segments of the bladder resulting from vesical neck obstruction.

DISCUSSION (*Abstract*)

Dr. H. Fay H. Jones, Little Rock, Ark—If one is to understand this subject thoroughly, he must be an anatomist and must be able to interpret his findings.

Hinman's classification says that the following three types of vesicle dysfunction are about all that are differentiated in the present state of our knowledge: (1) the paralytic bladder resulting from a frank lesion of brain or spinal cord; (2) cord bladder caused by an indefinite or latent lesion most likely to be in the spinal cord; (3) the atonic bladder caused by interference of peripheral nerves and often hard to distinguish from loss of tone or dilatation which results from mechanical obstruction.

In Dr. Orr's paper, of course, we are chiefly interested in the atonic bladder as the result of vesicle neck obstruction or hyperplasia of the vesicle neck.

In recent years the part played by the muscular involvement in the so-called vesicle neck, usually referred to as the internal sphincter, has assumed a much greater importance than was formerly given to it. Although the function of the nerves involved in micturition and the mechanism of micturition are not exactly known, theories have gained general acceptance in which the parasympathetic or sacral nerves are regarded as contracting or emptying nerves, and the sympathetic or presacral plexus in control of the internal sphincter is regarded as a group of filling nerves. Impairment of the parasympathetic or emptying nerves will cause retention of urine and continuous retention of urine from any cause will produce atony of the vesicle wall.

As you know, the internal sphincter, unlike the external sphincter, is not a circular construction of the vesicle orifices; but is an arrangement of considerable complexity which, I think, will probably be better understood in the near future.

According to Braasch and Thompson: "The factors involving sphincteric dysfunction are: (1) imbalance of innervation, with predominance of the sympathetic or filling nerves; (2) rigidity or failure of adequate relaxation of the internal sphincter referred to as dysectasia; and (3) apparent failure of coordination of reflexes involved in the act of micturition centering in the vesicle neck, to which the term of achalasia has been given. The first condition can be favorably influenced by presacral neurectomy and the second condition usually can be remedied by thorough transurethral resection."

There has been a great deal of literature on the treatment of sphincteric dysfunction caused by imbalance of the sympathetic or filling nerves by such men as van Duzen, Learmonth, Braasch and others. Last year Pierson, in an article in the *New England Journal of Medicine and Surgery*, gave a very enlightening discourse on the internal sphincter in a certain type of cord bladder, demonstrating the pathology and results of resection with urethrograms and cystograms.

It is important that the cystoscopist be alert as to his observations because he might overlook mild evidence of prostatic obstruction. Cystograms and cysto-metrography give one a very definite idea about the tonicity of the bladder. I feel that with cystograms as revealed by delayed pictures following intravenous urograms one does not get such clear-cut pictures of the bladder as with retrograde cystograms; just as intravenous pyelograms do not give such distinct pictures as do retrograde pyelograms. We have found that what was apparently a smooth bladder with delayed films following intravenous urography proved, with retrograde cystogram, to be a bladder irregular in outline.

The treatment of the condition that the essayist has just considered naturally means a removal of the hyperplastic cicatricial tissue at the neck of the bladder. Whether this be done by the direct vision punch with the McCarthy electrotome, Braasch, Bempert-Young or the Stern-Davis method, is practically immaterial to my mind. The operator should employ the technic which he has mastered to do his work to the best advantage. The main thing, after all, is to be able to remove the entire obstruction at the vesicle neck.

All of us have seen cases in which the bladder is very slow to return to normal function due to long-continued retention; and it is often necessary to resort to the use of a retention catheter for several days and intermittent catheterization over a period of weeks. Of course, as the tone of the bladder returns, one will note that the intervals of catheterization will increase and the amount of residual urine will decrease.

The last case presented by Dr. Orr on which he did a resection of a large portion of the superior surface of the bladder, is most interesting. I think his good results were no doubt due to the fact that he had not disturbed the parasympathetic nerves to any appreciable degree.

The atonic bladder is a subject inviting much study and research and one which will be the topic of much discussion during the next few years.

CONGENITAL POLYCYSTIC DISEASE OF THE KIDNEYS*

By HUGH R. SPENCER, M.D.
Baltimore, Maryland

The term, polycystic disease, is used to describe a congenital affection which results in the production of multiple cysts in the kidney and frequently also in the formation of cysts in the liver.

Bell,[1] in a comprehensive article, presents statistics to show that this disease is recognized clinically in one out of every 3,523 hospital admissions and that the lesions are found in one out of every 500 autopsies. At the University Hospital there have been seven cases in the past 1,600 autopsies, an incidence of 1:228.

The disease produces symptoms at one of two

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*From the Department of Pathology, School of Medicine, University of Maryland.

age periods, towit: either in young infants or in adults in or past the third decade. Statistics show that there is little difference in the incidence in males and females. In our series there were 3 males and 4 females.

Heredity plays a role in polycystic disease. Dunger[2] observed the disease in five siblings. Cairns[3] found ten cases in three generations of the same family and Shapiro[4] described the disease in a mother, in four of her children, and in one of her grandchildren. Goldstein[5] reports the disease in a woman and in four of her children, and in a man and in two of his children.

It is generally agreed that polycystic disease is the result of defect in embryological development. That it may be a part of a general embryological disturbance is suggested by the occurrence of genital anomalies, spina bifida, meningocele, club foot or polydactylism as associated lesions in some of the cases.

From reconstructions it has been shown that the kidney cysts are derived from the developing renal tubule and it is believed by Kampmeier that cyst formation is the result of a failure in complete involution of the first three or four generations (embryological) of the convoluted tubules.

The gross pathology of the kidneys is striking. The organs are usually enlarged, and although weights up to 3,000 grams or more have been recorded, the average weight of the cystic kidney in the adult is about 500 grams. There is frequently some difference in the size of the affected kidneys in a particular individual and in from 5 to 10 per cent of the cases the lesion is unilateral. The kidneys, in spite of marked enlargement, retain a relatively normal shape. The external surface is studded with rounded cysts. On section the cut surface presents a honeycombed appearance, the renal parenchyma is largely replaced by cysts which vary in size from 2 to 3 mm. up to 3 to 4 cm. or more in diameter.

The walls of the cysts are relatively thin and the cysts contain yellowish gelatinous material or a fluid which may be either clear, dark brown, or turbid. The fluid in the cysts is rich in urea and uric acid. Small greyish islands of renal parenchyma may be observed in the intercystic spaces. In the advanced cases these islands are most abundant in the subcapsular zone.

Histologically, the smaller cysts are lined by clear cuboidal epithelial cells, while in the larger cysts, as a result of pressure, the epithelium is often markedly flattened. Occasionally, glomeruli may be seen projecting into the cysts. The remaining renal parenchyma is compressed and throughout the kidney there is scarring. The arteries commonly show intimal thickening, and in the advanced cases with hypertension the arterioles are involved.

Not all polycystic kidneys produce symptoms; often in the new born and occasionally in adults the lesion is an incidental finding at autopsy. Moreover, symptoms are often lacking until late in the disease. The character and extent of the symptoms naturally depend upon the extent of the disease.

From the standpoint of pathogenesis, the characteristic feature is a progressive enlargement of the cysts, the lining epithelial cells continuously secrete, so that cysts which in the beginning were perhaps microscopic eventually become large. This progressive enlargement of the cysts produces a palpable mass in one or both flanks in 90 per cent of the clinical cases.

The pelves and ureters are pushed down and toward the midline, and the pelves are elongated. These are important points in the matter of pyelography. Although the cysts do not ordinarily communicate with the calyces, increasing pressure sometimes leads to actual rupture of the cyst wall and bleeding into a calyx results.

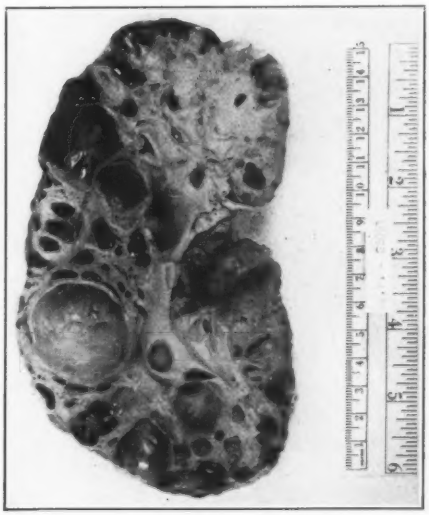

Fig. 1

Photograph of polycystic kidney, left. Weight of right and left kidneys in this case 645 and 600 grams, respectively. Patient, a colored female, aged 28 years.

Hematuria is an important symptom in 33 per cent of the cases. Occasionally an ascending infection leads to involvement and subsequent rupture of the cysts into the calyces. In these cases pyuria, pain and tenderness over the mass, and fever are important diagnostic points.

With the continuous enlargement of the cysts, the interspersed renal parenchyma, by pressure atrophy is progressively destroyed. The resultant symptoms are those of renal failure and the picture may simulate that of chronic nephritis. There is usually a marked decrease in the elimination of 'phthalein and a retention of nonprotein nitrogen in the blood. Persons with polycystic disease of the kidneys often develop an unusual tolerance to retained nonprotein nitrogen; these patients with a 'phthalein of from 5 to 10 per cent and a nonprotein nitrogen of 250 mg. or above often go on for months without the development of uremic symptoms. This is an important point in the differentiation between polycystic disease and chronic nephritis. Other evidences of a failure in renal function are a low fixed specific gravity and a mild albuminuria. Casts may or may not be found in the urine. Edema is rarely prominent.

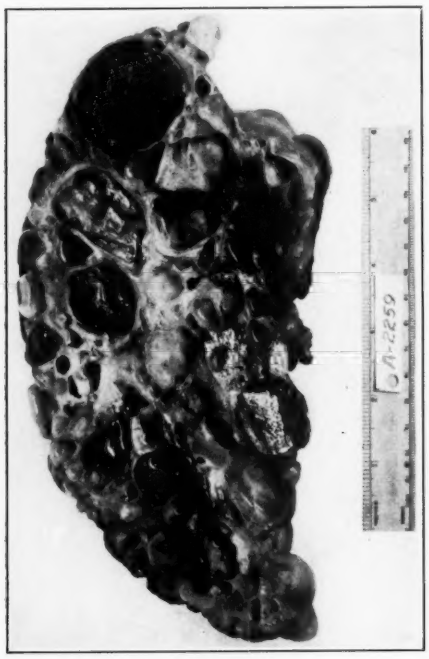

Fig. 2
Photograph of polycystic liver. Weight 4,000 grams. Right and left kidneys in this case weighed 370 and 320 grams, respectively. Patient, a colored female, aged 54 years.

Hypertension occurs in about 50 per cent of the cases; usually it is mild. The systolic pressure averages around 150 mm. Hg. In the more advanced cases pressures of 175 mm. Hg. and above have been recorded; however, extremely high pressures are unusual. Cardiac hypertrophy in these cases bears a definite relationship to hypertension. In about 50 per cent of the recorded cases, some enlargement of the heart has been noted. The average weights of these hearts at autopsy have been less than 450 grams. Marked cardiac hypertrophy is rare. Death is usually due to renal insufficiency and the large majority of these people die in uremia. The duration of life following the onset of symptoms may be from one year to, in exceptional cases, as long as twenty years.

In about 30 per cent of the cases of polycystic disease, the liver is affected. The extent of the involvement varies. Occasionally, there are a few scattered cysts in a liver of normal size; in other instances the liver is tremendously enlarged, the surface is studded with projecting cysts and the parenchyma is honey-combed. Here, as in the kidney, cyst formation is thought to be due to an embryological disturbance.

Where the cysts are few, clinical symptoms attributable to the liver are absent; however, with extensive involvement, the liver becomes a large nodular mass suggesting metastatic carcinoma or echinococcus cysts. Pressure of the cysts may obstruct the portal circulation and lead to ascites. In one of our cases ascites was one of the prominent features. Jaundice is apparently rare.

The diagnosis of polycystic disease depends upon a number of fairly characteristic findings:

(1) A palpable mass in one or both flanks which may or may not be associated with enlargement of the liver. Occasionally, the mass may be the only prominent clinical feature as in certain cases in the fetus and in the new born. The earliest symptom in one of our cases was a large mass in the upper abdomen.

(2) Evidences of renal failure; prominent among which are albuminuria, low fixed specific

gravity, low 'phthalein output, and a high non-protein nitrogen that is relatively well tolerated.

(3) Intermittent attacks of gross hematuria, which occur in one-third of the cases. Occasionally blood clots caught in the ureters give the clinical signs of renal calculus.

(4) The pyelogram. Pyelographic examination frequently offers conclusive evidence of the existence of polycystic disease. Errors in interpretation are not at all uncommon when single pyelograms are made. Bilateral pyelography is very important since renal tumors rarely occur on both sides, while polycystic kidneys practically always do. Because of low renal function, intravenous pyelography is usually not satisfactory. The characteristic changes are:

(a) Elongation of the pelves and major calyces with blunting of the minor calyces.

(b) Right angulation of the ureter in its relation to the pelvis.

(c) Displacement of the ureter toward the midline.

(d) Bilateral pelvic changes.

SUMMARY

(1) Polycystic disease of the kidneys is a congenital affection characterized by the formation of multiple cysts in both kidneys and in the liver in 30 per cent of the cases.

(2) The incidence is about 1:3523 hospital admissions and 1 every 500 autopsies. There is no difference in sex incidence. The disease is seen in the new born and in adults in or past the third decade.

(3) The disease results from embryological maldevelopment.

(4) Symptoms are directly or indirectly the result of a progressive pressure atrophy of renal parenchyma or of infection.

(5) The important clinical findings are: Mass, urinary changes characteristic of renal failure, decreased 'phthalein output, a well tolerated non-protein nitrogen retention, intermittent hematuria, and hypertension.

(6) The pyelogram is usually characteristic.

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A CASE OF LIPOPHAGIC GRANULOMA AND SCLEREMA NEONATORUM*

By F. J. EICHENLAUB, M.D.
and
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The patient was a colored female, born October 14, 1933, at Gallinger Municipal Hospital; tenth child; full term; normal delivery; requiring no artificial resuscitation; birth weight nine pounds. There were nine living children of the parents and no similar lesions had been observed in any of the other infants. On the fourth day after delivery, the obstetrical intern first noticed indurated areas in the skin (*Fig. 1*).

When seen in consultation on the sixth day, there were present twelve indurated, painless, circumscribed, fairly symmetrical areas, not adherent to the underlying structures, varying in size from 0.5 to 3.5 cm., limited to the upper back and extensor surface of both arms. The skin over these masses was livid in color, smooth and not elevated. This induration of the subcutaneous tissue would not "allow the skin to be pinched up in folds." In the photograph one of these areas can be seen held between the thumb and index finger of the intern.

All laboratory and x-ray examinations on mother and child were negative. The general condition of the child was good until the twentieth day, when a left otitis media developed, which was soon followed by involvement of the right ear. This was accompanied by an irregular fever. On the twenty-fourth day there was clinical evidence of a lobar pneumonia and the infant died when twenty-seven days old. Some of the subcutaneous infiltrations showed definite evidence of involution by softening and a few of the smaller lesions had almost completely disappeared before death.

Four days before death practically the entire skin surface became firm and diffusely infiltrated. The process began in the legs and spread over the body. There was no change in the surface appearance, but to palpation the skin was firm, resistant, and wax-like. It did not pit on pressure. When one attempted to pick the skin up, it was done with difficulty and there was no normal pliability nor easy wrinkling.

Postmortem Report.—(By Dr. H. H. Leffler, who also prepared many of the sections herein presented and described.)

The lungs weighed forty-five grams each. The right showed consolidation of the upper part of the lower lobe and the upper part of the upper lobe. The left lung showed consolidation of the lower part of the lower lobe and the upper part of the upper lobe. The middle lobe was free from inflammation. The lungs were suspected of being pneumonic, and such a gross diagnosis was made. "Histologically there was marked conges-

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*From the Department of Dermatology and Syphilology, Georgetown University School of Medicine.

Fig. 1
Photograph of child showing subcutaneous indurations.

tion. The interstitial tissue was swollen and the alveolar spaces were markedly encroached upon. There was fluid in some of the alveolar sacs as well. The interstitial tissue contained an increase of mononuclear cells, many of which were vacuolated. During life they may have contained fat. The question of fat emboli to the lungs was considered, but many sections stained for fat failed to disclose its presence."

The brain was markedly congested. The nerve cells did not appear to be acutely injured.

The middle ears contained a small amount of seromucous material. The mastoids were uninvolved.

The adrenals were of normal position and appeared normal grossly as well as histologically. The fat about the adrenals showed many irregular spaces. In one area there was a small hemorrhage. From the configuration of these spaces it would appear that they contained fluid during life and that there were recent cavitations in the fat about the adrenals. There was, however, no important inflammatory reaction. It is thought that the cause of death in this case was possibly a septicemia following otitis media and mild bronchopneumonia.

Sections of the indurated areas of the skin were of particular interest.

Histology.—(High and low power photomicrographs, *Figs. 4* and *2*). The epidermis and cutis were essentially normal. The dermal layer contained the normal amount of connective tissue in which were seen the usual blood vessels, nerves, sebaceous glands and hair follicles, none of which was abnormal. The disease involved the entire thickness of the subcutaneous fat tissue. It showed large areas in which there was an extensive infiltration with giant cells of the foreign body type; epithelioid cells; small round cells and plasma cells. Many of the interlobular fat septa showed a great thickening composed of the same infiltrate of giant cells, epitheliod cells, round and plasma cells.

In some of the granulomatous areas the fat cells contained many needle-like crystals in the form of rosettes. These crystals were also observed in the giant cells themselves. The process is essentially a granulomatous infiltration of epithelioid and foreign body giant cells.

SUBCUTANEOUS FAT NECROSIS

The symptoms of this disease are markedly similar in the reported cases. As already described, the areas are indurated, circumscribed, painless, fairly symmetrical, unattached to the underlying structures and vary in size from a split pea to large areas covering the greater part of the back and buttocks. The lesions of subcutaneous fat necrosis have occurred principally on the exposed parts such as the cheeks, chin, back, buttocks and deltoid region. Softening of the areas usually begins from the fifth to the sixth week and is complete as a rule in three to six months. The lesions disappear completely and only in rare instances do they leave any trace such as atrophy. The infants affected are usually healthy normal babies. The lesions appear two to twenty days after birth. The recorded deaths have usually been due to some intercurrent disease.

Etiology.—Most authorities agree that trauma

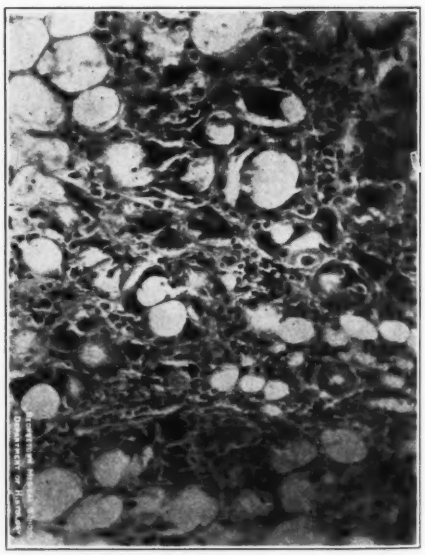

Fig. 2
High power photomicrograph showing areas of extensive infiltration with giant cells, round cells and plasma cells; and needle-shaped crystals.

is the most important etiologic factor. "An anemia of local areas caused by compression against hard underlying structures during birth and too vigorous methods of resuscitation" have been considered as etiologic. It should be noted that there was no birth trauma except that caused by the size of the infant in this case, and no resuscitation was used. Subcutaneous fat necrosis has been produced experimentally by traumatization of the skin of young pigs and other animals.[1 2]

The exact mechanism of fat necrosis is not understood. It is possible that the necrosis may be due to a ferment liberated from leukocytes by trauma, or to some toxic factor. The chemical composition of the crystals present has not been agreed upon. Some contend that the crystals are composed of a palmitin-stearin mixture while others consider them cholesterol esters.

It will be seen from this description that this patient presented two conditions. The first to develop was the typical picture of lipophagic granuloma (subcutaneous fat necrosis), a diagnosis confirmed by biopsy before the more serious condition developed. The second and probably unrelated disease developed after otitis media and probable bronchopneumonia caused inanition and dehydration. This, we be-

Fig. 4
Low power photomicrograph showing great thickening of interlobular fat septa; infiltration with giant cells, round cells and plasma cells; small needle shaped crystals.

Fig. 3
Low power photomicrograph of section stained with Sudan 3. Cutis entirely normal.

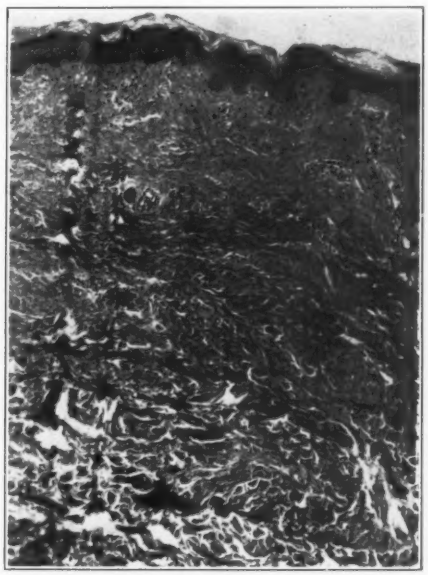

Fig. 5
Low power photomicrograph of case of scleroderma (for comparison) showing hypertrophy of the collagenous tissue of the skin and subcutaneous tissues. The fat is replaced with sclerotic tissue.

lieve, was a true sclerema neonatorum, and, so far as we can find, this is the first instance of both these diseases' occurring in the same patient. We can find no other case of lipophagic granuloma (subcutaneous fat necrosis) which came to postmortem.

DISCUSSION

Since the paper of Howard Fox[3] called attention to subcutaneous fat necrosis, there has been an increasing number of cases of this disease reported. In his paper Fox offers a very good classification of the infiltrative skin diseases of the new born. In spite of this report, however, there is still a very great deal of confusion in the foreign literature, and in the pediatric literature of this country, as to the proper classification of cases reported. The terms sclerema neonatorum, scleroderma neonatorum, scleredema, and subcutaneous fat necrosis are indiscriminately applied to disease processes which neither clinically nor pathologically fit the names.

We believe the following classification, in part that proposed by Fox and added to and defined by our experience with the case here recorded and with various cases described under different names in the literature on the subject, will help to clarify the confusion that now exists.

(1) *Edema Neonatorum.* — This is simple edema of the skin complicating constitutional disease in the new born infant, such as acute infections or cardiac and renal disease. The skin is thickened and edematous without evidence of inflammation, in the independent portions, usually the back, buttocks, and legs. Pitting on pressure is always present. Histologic examination shows nothing but edema of tissues.

(2) *Scleredema Neonatorum.*—This is a diffuse superficial infiltration of the skin occurring after various infectious diseases. It starts on the neck, spreads over the face and down on the shoulders, chest, and back. The skin has a smooth appearance, does not wrinkle or fold normally or easily, and feels definitely spongy to the touch, though pitting on pressure is absent. Because of the infiltration the face may assume a mash-like appearance. There is no atrophy or pigmentation. The disease is self-limited, usually gradually disappearing in from a few days to a few months. Buschke[4] has reported similar cases in adults, some of which lasted a year or more.

Freund[5] described the microscopic picture:

> "Most prominent feature is an enlargement of the collagen bundles to several times their normal size. This produces a thick layer in the deeper portion of the corium and throughout the subcutaneous tissue. The collagen bundles are edematous and there are few connective tissue cells among them."

In the only case of scleredema which we have had an opportunity to study, there was definite swelling and edema of the collagen bundles. However, changes in the collagen tissue are difficult to interpret and we do not believe these changes to be sufficiently marked to be pathognomonic.

(3) *Scleroderma Neonatorum.* — In infants this disease presents all of the characteristics seen in older patients. Because of the slowness of its development, a definite diagnosis could probably not be made for some months until all the typical features have had time to develop or a classical histologic picture to be found.

In a typical scleroderma there is hypertrophy of the collagen tissue of the skin and subcutaneous tissues. The fatty tissue is replaced by sclerotic tissue. In the early edematous stage there is a rich inflammatory infiltrate. The disease usually occurs in patches, and presents in addition to the infiltrative characteristics defi-

CLASSIFICATION OF INFILTRATIVE SKIN DISEASES

Disease	Pitting	Distribution	Pigmentation Atrophy	Inflammation	Histologic Picture	Prognosis
Edema Neonatorum	Present	Dependent portions	Absent	Absent	Edema	That of cause
Scleredema Neonatorum	Absent	Neck, face, upper body	Absent	Absent	Enlargement of Collagen bundles (edema)	Good, self-limited
Scleroderma	Absent	Anywhere	Present	Present early Absent later	Characteristic	Poor, incurable
Sclerema	Absent	Legs upward	Absent	Absent	Not characteristic	Poor, patients usually die
Lipophagic Granuloma	Absent	Back, cheeks, arms, thighs	Pigmentation absent, occasionally atrophy	Present	Characteristic	Good, self-limited

nite atrophy and pigmentation. Scleroderma neonatorum is a very rare disease. It is essentially a disease of the connective tissue, and not of the fat.

(4) *Sclerema Neonatorum.*—This is a disease of the subcutaneous fat seen exclusively in infants suffering from inanition with dehydration. Usually the skin of the calves is first affected and the process spreads upward to involve the other parts of the body. The palms, soles and scrotum are not affected. The areas affected show a diffuse infiltration, the skin has a waxy appearance and feels cold to the touch, but there is no pitting on pressure.

As in our case, the skin is hard and dry and no fluid escapes. Although cases have been reported[7] demonstrating evidence of chronic inflammation in the subcutaneous fat, our sections were negative microscopically.

Knopfelmacher[7] concluded that the disease was made possible by the fact that the fat of new born infants contained approximately 20 per cent less oleic acid than in later life, while the palmitic and stearic acids, which congeal at a higher temperature, are present in greater amount in the nurslings. Most of the patients die, so that the ultimate condition of the skin is not known. These symptoms seem to be due to change in the character of the skin fat. There is a solidification of the fatty tissues, probably due to insufficient fluids.

(5) *Lipophagic Granuloma* (*Subcutaneous Fat Necrosis*).—These cases have been clearly described by Fox[3] and a typical case is reported above, so that further description is needless. In view of the pathologic findings of our case, of other reported cases, and of Fox's description, we feel that the point made by Weidman in discussing Fox's paper and by Fraser[6] in discussing another case, is well taken. If it occurs at all, true necrosis must be rare, and perhaps a secondary change. We feel, therefore, that lipophagic granuloma is a better term for this disease. However, precedent usually decides these matters, and it is not an important point.

CONCLUSION

(1) A case of combined lipophagic granuloma and sclerema neonatorum is reported.

(2) A classification and nomenclature for this group of diseases is proposed.

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DISCUSSION (*Abstract*)

Dr. Thos. W. Murrell, Richmond, Va.—This is a rare case. Under the heading, "Ischemic Fat Necrosis," in the *Annals of Surgery*, May 1923, C. E. Farr reported a somewhat similar case which recovered.

In the investigation of this condition some original work was done, which seemed to prove that trauma was the etiological factor. Farr described six other cases in adults of nodules after trauma, which terminated either in cyst formations or calcareous deposits. He presented these as additional evidence in support of the theory of trauma causation.

Farr's baby had gone through a long and hard instrumental labor, but in the case just presented trauma can hardly be expected, since the patient was the tenth child and a normal delivery. This would seem to prove that some other factor must be present.

Dr. Eichenlaub is to be thanked for his classification, which should be an aid in diagnosis and in teaching.

Dr. M. T. Van Studdiford, New Orleans, La.—This condition has been thoroughly investigated by Dr. Howard Fox. It is interesting, but the obstetrician and pediatrician usually fail to consult with the dermatologist and therefore the rank and file of dermatologists have little opportunity for studying these little patients.

Dr. Eichenlaub (closing).—Our purpose in presenting this paper was two-fold: (1) To place on record an unusual combination of two diseases of the new born occurring in the same infant; (2) To present a classification of this group of diseases which we hope will help clear the confusion that at present exists in the infiltrative diseases of the new born.

HISTOPATHOLOGIC STUDIES OF THE BRAIN IN DELAYED DEATH FOLLOWING STRANGULATION*

By FERDINAND C. HELWIG, M.D.
Kansas City, Missouri

Many elaborate studies have been conducted by a number of investigators on the clinical and pathological findings in asphyxia from different causes. The finer microscopic changes found in the brain following asphyxia have also been thoroughly investigated, particularly in carbon monoxide death and immediate death resulting from other types of asphyxia. Spielmeyer[1] and his associates, as well as other writers, have

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observed and carefully studied the morphologic changes in the brain brought about by vascular alterations, particularly those observed in epilepsy.

Delayed death following acute mechanical asphyxia, however, has not been the subject of any considerable literature. Quite recently Döring[2] has studied the brain in a case of delayed death following hanging and also in a case of death following ligation of the carotid artery. Wustmann and Hallervorden[3] have investigated the finer morphologic details produced in the brain following delayed death from massive pulmonary embolism in which the Trendelenburg pulmonary embolus operation was performed. These two studies in particular along with those of Scholz[4] on epilepsy constitute the most recent and interesting studies which I have been able to find in the literature. Because these delayed deaths have been the subject of little study it seemed worth while to report the following case:

Case History.—Mr. H., 54 years of age, entered the hospital because of a hard, indurated mass beneath the left mandible which followed a small ulcer on his lip. This mass had the typical palpatory consistency of a metastatic carcinoma. It was firmly fixed and apparently involved the submaxillary lymph nodes. Physical examination was otherwise essentially negative except for a blood pressure of 180-110. The patient was a very well developed, well nourished white man, a farmer by occupation, who had never been seriously ill in his life. A block dissection of the neck was done in the morning under local anesthesia and the patient was transferred to his room. The operation lasted one hour and twenty minutes. About 3:20 in the afternoon the patient, who was perfectly conscious and feeling quite well, rose to a sitting posture to take a drink of water. He choked while swallowing the water, became very cyanotic and began to struggle for breath. I was immediately summoned and within ten minutes after his cyanosis first began I inserted a tracheotomy tube. The trachea was pushed far over to the right and a large mass of blood was found markedly displacing the trachea. The patient had not breathed at any time during the period since the tracheotomy tube was inserted, a period of exactly ten minutes. Moreover, for a period of over three minutes we could not feel the pulse at the wrist or hear his heart beat with the stethoscope. The patient was almost purple in color. He was given artificial respiration for a period of about ten minutes, when he began to breath spontaneously. About three minutes after starting the artificial respiration a faint pulse was perceptible. After the insertion of the tracheotomy tube, air passed readily into the lungs and carbon dioxide and oxygen were given through the tracheotomy tube for a short period. Within an hour after his revival, his pulse was 94 and the respiration was 16 per minute and somewhat irregular in character. The patient did not regain consciousness. About 5:00 o'clock in the evening he began to have minor convulsions. These became progressively more severe. Clinical tests for paralysis were negative. There were no signs of intracranial hemorrhage. At 6:15, almost exactly three hours after his initial respiratory and cardiac suspension, he began having very severe convulsions and died in a convulsion which lasted about five minutes.

The only clinical abnormality observed in the patient between the time that he was revived by tracheotomy and artificial respiration and his convulsions two hours later, was the fact that at no time did he regain consciousness.

The lymph nodes of the neck showed typical squamous cell carcinoma.

His autopsy was essentially negative except for the tracheotomy incision on the right side of the neck, moderate generalized arteriosclerosis with a mild chronic arteriolarsclerotic nephritis and some cardiac hypertrophy. The lungs were freely crepitant and expanded. The trachea and bronchi were clear. Microscopic examination of the viscera showed myocardial hypertrophy and fatty changes in the liver. A moderate degree of arteriolarsclerosis was present in the kidneys. The prostate showed benign adenomatous hypertrophy.

On opening the skull, the brain showed an apparent decrease in the subarachnoid fluid. On repeated cross section there was moderate hyperemia of the smaller vessels throughout the white substance. This, however, was not striking. Very careful examination of all sections revealed no petechial hemorrhages, blanching or softening. The vessels at the base of the brain showed some atherosclerotic plaques. Otherwise the brain was essentially negative on naked eye examination.

Microscopic Pathology.—Sections were taken from the frontal, central and striate cortex, Ammon's horn, putamen and globus pallidus, external geniculate body and several other areas and stained with Nissl, myelin, Herxheimer, Bielschowsky, sudan and hematoxylin-eosin preparations.

The most striking changes were observed in the ganglion cells of the cortex which, with the Nissl stain, revealed alterations of a diffuse degenerative character that were more or less uniform in all the regions studied. Many of the ganglion cells did not take the Nissl stain well and there was a decided tendency in many instances to show a loss of Nissl granules or else a breaking up of these granules into fine dust-like particles. The contour of the cells was strikingly altered in many instances. Some of them were rounded in character, while others were shrunken and varied in shape from round to oval and even a triangular configuration. In many instances the nuclei of the ganglion cells were considerably swollen and assumed a much darker stain than normal. In many of these cells containing the dark nuclei the ganglion cell cytoplasm took on a diffuse pale bluish, uniform stain which was interpreted as representing an early ischemic degeneration while the granular transformation and alteration of shape and size of the cells seemed to be associated with a more advanced ischemic degeneration. Not infrequently there was a tendency to formation of a pale, clear zone around the nucleus in some of the ganglion cells; this represents the so-called "Wasserveranderungen."

In Ammon's horn there was no loss of cells in Sommer's sector, but the ganglion cells presented the same faint staining characteristics of the cytoplasm and breaking up and loss of Nissl's granules previously observed.

The globus pallidus appeared normal. In the frontal cortex, in addition to the changes previously described, some of the ganglion cells in the fifth and sixth layers showed marked shrinkage. In addition to these ganglion cell changes there were both progressive and regressive changes in the glial cells, with a definite increase in the number of macroglia (astrocytes), many of which contained bluish green cytoplasmic granules. Some of the large pyramidal ganglion cells contained fat and the bluish green granules observed in the macroglia with the Nissl stain were seen to take the sudan stain. Progressive macroglia and regressive microglia changes were quite notable in the molecular layer of the cortex.

In the white matter the blood vessels occasionally showed perivascular round cell infiltration and some cells containing fat were also seen in the Virchow-Robin spaces. Lipoid stains likewise revealed the presence of fat in the walls of many of the capillaries of the cortex and this was likewise seen at times in cells embedded in the pia-arachnoid. In the Bielchowsky preparations the shrunken cells observed in the Nissl stain often showed argentophilia of the nuclei and occasionally coalescence and fragmentation of the neuro-fibrils of the cell body.

DISCUSSION

One of the most important factors to be considered in the evaluation of the changes which take place in the nerve cells is the establishment, if possible, of the time interval during which complete asphyxia with cessation of heart action can be present without producing irreversible changes in the brain which may lead to the subsequent death of the individual. Partial asphyxia naturally may produce the clinical picture of apparent death and it has been stated that individuals who have been completely submerged in water for as long as one hour may be resuscitated. Moreover, it is not at all rare to find instances in which newborn infants have been resuscitated after apparent asphyxiation over rather long periods during which both pulse and respiration had ceased. However, these factors are quite variable. I have gained the impression from a large number of necropsies on stillborn and newborn infants very shortly after birth where evidence of massive amniotic aspiration was present that the occurrence of such a type of aspiration had led to death when the period of aspiration had been rather brief. Moreover, in many of these instances it was apparent that no definite abnormality of labor was present and yet massive aspiration with all signs of asphyxia occurred shortly after birth. The great frequency of this finding at necropsy suggests that the survival occurred in those cases in which there has been only partial asphyxiation.

The investigations of Wustmann and Hallervorden[3] are of great importance in solving the time interval factor. These authors recorded six instances in which the Trendelenburg embolus operation was performed. Three of these patients lived for several hours after the operation. A brief review of these three cases seems worth while.

Case 1.—A man 62 years of age underwent a suprapubic cystotomy operation for a large prostate. He developed first a pulmonary infarct and later a massive embolus. Trendelenburg's incision was made five minutes after the embolism lodged, and eight minutes after lodgment the embolus was extracted. The patient developed amnesia, lung edema, left-sided hemiplegia, wandering speech, and died eleven hours and twenty minutes later.

Case 2.—The patient, aged 55, was operated upon for drainage of a perforated appendix. A massive embolism developed. Six minutes later the Trendelenburg incision was made. Eleven minutes later three thrombi were removed from the pulmonary artery. Twenty-five minutes after the removal of the emboli the patient took his first spontaneous breath. Pronounced central nervous system manifestations soon developed and a bilateral Babinsky was observed. Clonic convulsions in the right foot and arm soon developed. Tetanic convulsions then ensued and the patient died.

Case 3.—The patient, aged 63, had a nephrectomy for a pyelonephrotic kidney and ureteral stone. Twenty-four hours later a pulmonary embolus occurred. Within fifteen minutes the Trendelenburg operation was started and a 52 cm. thrombus was removed six minutes later. Four minutes later the radial pulse was obtained and spontaneous respiration started. Fifteen minutes after the beginning of the operation regular respiration was observed. Some of the reflexes returned, the patient groaned loudly, moved his hands but remained unconscious. Later he developed Cheyne-Stokes respiration and nineteen hours after the Trendelenburg operation he died. In this case the heart did not beat for six minutes and the patient did not breath for sixteen minutes.

In all three autopsies ischemic changes were observed in the ganglion cells of the cortex, which alterations were also present in the Purkinje's cells of the cerebellum.

These authors were of the opinion that irreversible changes took place in the brain if a period of five minutes or more elapsed in which there was no spontaneous action of the heart, and considered that the only method of saving the patient with pulmonary embolism was to speed up the time of removal of the embolism.

It is interesting in this respect that Leawen and Sievers[6] found, in their experiments on rabbits, that pulmonary arterial obstruction caused death if it lasted two and one-half minutes. However, they were able to revive the animals by artificial means when the obstruction had been prolonged as much as seven or eight minutes. In Nystrom's[5] cases surviving the Trendelenburg operation 60, 65, 104, 75 and 105 seconds intervened before the obstruction was relieved and it is Nystrom's opinion that under favorable circumstances a complete stoppage of circulation for as much as two minutes is not necessarily incompatible with life. Of Nystrom's two cured cases, one had survived one year and the other two years at the time of his published article. These two patients apparently showed no central nervous system sequelae. One of these patients had complete circulatory suspension for 104 seconds, the other for 105 seconds.

Crafoord's[6] case was unconscious for several hours following the operation and was delirious and blind. On the third day after the embolectomy sight returned and her cerebral symptoms vanished, but in this instance the complete obstruction had lasted only about forty to forty-five seconds.

Similar changes to those observed by Wustmann and Hallervorden[3] were seen by Döring,[2] who recorded a death which was delayed 96 hours after hanging and one 58 hours following ligation of the right common carotid artery. In these instances they observed necrosis in the cerebral cortex and main ganglia. These necrotic foci were not symmetrical and appeared as punctate or somewhat larger areas of cortical bleaching. In both instances severe degenerative changes were encountered in the globus pallidus and this finding was bilateral in the case of hanging.

In the case where carotid ligation had taken place only the right side showed these changes. In the ganglion cells they found not only the typical ischemic cellular changes described by Spielmeyer, but likewise homogeneous ischemia and very severe cellular changes. The glial tissue showed chiefly regressive manifestations.

Deutsch[7] also recorded a case of delayed death following hanging in which the patient lived three months before he finally succumbed. Symmetrical softening was encountered in the corpus striatum and lenticular nuclei without alteration of the cortex or thalmus. Bingel and Hempel[8] likewise reported a case that died seventy hours after hanging in which both progressive and regressive glial changes were found. Degeneration was seen in Ammon's horn and in the Purkinje cells of the cerebellum, while the globus pallidus appeared quite normal. Scholz[4] mentioned, in a recent study on epilepsy, an instance of delayed death following hanging in which ischemic cellular damage was observed in the cortex and Purkinje cells.

G. Müller[9] recorded two instances of delayed death from carotid ligation, one forty-five and one four days after the ligation. In the brains of both cases scattered degenerative foci were observed. The most striking changes in these cases were seen in the third cortical strata and consisted of ischemic ganglion cell changes often with alteration in the Nissl substance and both progressive and regressive alterations in the glia.

SUMMARY

The case I have recorded showed earlier histological changes in the brain than any of the cases obtained from the literature. There were no foci of blanching or softening, such as were described in several of those cases, and all of them had progressed over a much longer period of time than my case. Nevertheless, the changes described in my case seem to be consistent with the short clinical duration of the process, so that the classical picture of advanced ischemia would not be present. It appears from an analysis of the findings that the changes in Nissl substance in the Nissl preparations, as well as ganglion cell alterations observed particularly with the Sudan and Bielchowsky stains, could, for the most part, be accounted for on the basis of ischemia. Moreover, the clinical course suggests that these changes, even when they have only progressed to the extent described in this recorded case, are irreversible and inconsistent with life.

CONCLUSIONS

(1) A case of delayed death following strangulation is recorded in which early ischemic changes of the brain cells are described.

(2) An attempt has been made to show that cerebral ischemia from complete circulatory suspension can be maintained for only a very short interval before irreversible changes take place

in the cells of the higher centers of the brain that result fatally for the patient.

(3) Complete circulatory stoppage was apparently present in this reported case for a period of approximately six minutes with an added factor of marked anoxemia from strangulation for a period of about ten minutes. Following tracheotomy the patient developed a normal heart rate and rhythm as well as spontaneous respiration, but never regained consciousness and died after a period of three hours in a major convulsion.

The author wishes to thank Dr. A. T. Steegmann, of the City Hospital, Cleveland, Ohio, for his technical assistance, painstaking study of the sections of the brain and helpful suggestions regarding the interpretation of the histologic findings.

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DISCUSSION (*Abstract*)

Dr. Chas. C. W. Judd, Baltimore, Md.—Dr. Helwig has investigated the minutiae of histological alterations of the cerebral structures that result in ultimate death from strangulation, but he has emphasized the rapidity with which these changes occur.

He has also stressed the distinction which should be made between sudden and complete occlusion of the cerebral circulation, and the equally sudden but not absolute cessation of circulation of the brain.

He has made plain the extreme emergent character attendant upon the successful treatment of both forms of cerebral anoxemia and yet made clear that the time element is to be measured in seconds for complete occlusion and minutes for incomplete one. He emphasizes the necessity of instantaneous intervention to obviate irreversible damage to the brain in cases of strangulation.

It is obvious from the case reported that microscopic changes are not necessarily present in irreversible damage to the cerebrum due to anoxemia. What I am not quite sure of is this: what is the minimum microscopic alteration of irreversible degeneration which is incompatible with life? Has Dr. Helwig come to any, even tentative, conclusion on this point?

PREMATURE INFANTS*

A CLINICAL STUDY OF 432 INFANTS BORN PREMATURELY

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The problem of infants born prematurely is a very real one. The present high mortality rate among this class of infants constitutes a challenge in the field of preventive medicine which cannot be ignored. Medical supervision of an active newly-born hospital service carries an added responsibility if for no other reason than that of mere numbers alone. With this idea in mind we have reviewed our results in the cases of four hundred and thirty-two premature infants admitted to the University of Virginia Hospital. We were stimulated further to make this study and to record our findings because of a rather drastic departure from a rule supposedly fundamental. Only a few of the infants included in this report were exclusively breast fed and a very large proportion received no breast milk. Our reasons for not conforming to the conventional and accepted method of feeding will be discussed under a separate heading.

We have considered as premature every infant weighing 2,500 grams or less and have included in this report every such infant admitted to our nursery breathing, no matter how low the birth weight, or what the degree of prematurity was as determined by the obstetrical history.

In order that this series of cases may be properly evaluated, a brief description of the facilities available for the reception of these infants and certain facts concerning their routine care would seem advisable. In the University of Virginia Hospital all infants, full term and prematures alike, are under the care of the Pediatric Department from the time they leave the delivery room. Nursery arrangements have been most inadequate and overcrowding has been the rule. There have been no special arrangements

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for premature infants. The infants described in this report spent their early days in the hospital in a small wash room adjoining our main nursery. Here all full term infants receive their daily baths and all other necessary treatments. We have enjoyed no special apparatus for the regulation of body temperature such as heated bassinets and incubators. For regulation of body temperature we have depended solely on premature jackets, hot water bottles, blankets and an electric heater of the ordinary reflector type. To a graduate nurse trained for this purpose is entrusted the nursing supervision of all newly-borns. Working under her direction is a constantly changing group of student nurses who of necessity do most of the actual handling of infants. For teaching purposes infants are assigned to changing groups of medical students and these students under certain restrictions of nursery routine have free access to the nursery.

FEEDING

A most important single factor in the care of premature infants is that of feeding. This of necessity includes not only the kind of food but also amounts and methods of administration. When one reviews the literature on this subject there is almost complete agreement as to the kind of food to be given, and that food is breast milk. So strongly has this been stressed that one might even hesitate to consider any other type of feeding except in cases of absolute emergency.

Due to certain policies of hospital administration existing for a period at our institution it became almost impossible to provide premature infants with breast milk unless they were sufficiently vigorous to nurse their own mothers. Since this is neither wise nor safe except in the cases of the more vigorous infants we resorted to the more or less routine use of artificial feedings. We confess that we began this practice with considerable misgiving. In selecting a substitute for breast milk our previous experience with whole lactic acid milk in full term infants suggested the use of this type of formula. If artificial feeding is to be successful it must fulfill certain requirements: (1) it must be easily digestible; (2) it must be available in a concentrated form; (3) it must be clean; and (4) it must permit of proper growth and development. It has been our experience that lactic acid milk fulfills the first three requirements unusually well. So far as the hospital stay is concerned, growth and development of babies fed lactic acid milk has been most astonishing. We have, in fact, found this method of feeding so satisfactory that at the present time it is rare for a small premature infant admitted to our nursery to receive any breast milk.

The lactic acid formula routinely used was that suggested by Marriott consisting of whole milk 16 oz., U. S. P. lactic acid, one dram, and one ounce of corn syrup. This formula was fed undiluted and furnished approximately twenty-seven calories to the ounce. Feedings were begun twelve hours after birth, the amount given depending, of course, on the infant in question. The amount fed over the twenty-four hour period was gradually increased until the infant received 80 to 100 calories per pound of body weight. The interval of feeding varied with the infant. The more vigorous were fed every four hours and the smaller and less vigorous every three hours. Occasionally two-hour intervals were necessary in the low weight brackets.

Methods of feeding are of great importance and contribute greatly to success or failure. We permit only the more vigorous babies to nurse at the breast and this is discontinued in favor of lactic acid milk when nursing entails too great an effort on the part of the infant. The more vigorous babies which are artificially fed nurse an ordinary narrow neck nursing bottle or Breck feeder. When the act of sucking and swallowing is associated with considerable effort on the part of the baby such infants are fed by a medicine dropper or by gavage. We have found gavage feeding to be a life-saving procedure and properly carried out by skilled nurses is safe and less fatiguing to the infant than any other method of feeding. Not infrequently a large and apparently vigorous premature fed from a bottle for no apparent reason will show a stationary weight curve or actual losses from day to day. In many instances immediate improvement with prompt gains in weight follows gavage feeding.

The value of small and often repeated transfusions is too well known to need any discussion at this time. This method of therapy should not be reserved for those infants showing anemia of various grades. We frequently employ transfusions in a more or less empirical fashion when for various reasons progress is not satisfactory.

Table 1 shows the comparative progress of infants graduating from the hospital arranged according to type of feeding.

Only eleven infants were exclusively breast

Table 1

Feeding	No. Cases	Average Birth Weight	Average Discharge Weight	Average No. Days in Hospital	Average Daily Weight Gains
Breast Milk	11	2181.6 Gm.	2243.3 Gm.	14.4	3.5 Gm.
Whole boiled Milk	6	2260.0 Gm.	2300.8 Gm.	15.6	2.6 Gm.
Breast Milk and Lactic Acid Milk	179	2233.9 Gm.	2333.8 Gm.	17.4	5.7 Gm.
Lactic Acid Milk	90	1873.6 Gm.	2482 Gm.	40.8	14.8 Gm.

fed. Ninety infants were fed exclusively on lactic acid milk, and one hundred and seventy-nine fed breast milk. Of the one hundred and seventy-nine fed breast milk complemented with lactic acid milk in many instances the amount of breast milk received was negligible. Table 2 shows the extent to which this was true.

Table 2

Number Cases	Number discharged on Lactic Acid Milk	Number discharged on Breast and Lactic Acid Milk	Number discharged on Breast alone
172	68	97	8

Of one hundred and seventy-two infants so fed, sixty-eight were discharged on lactic acid milk alone and only eight on breast milk alone. Of ninety-seven infants discharged on breast milk complemented by lactic acid milk it is safe to assume that breast milk was discontinued shortly after discharge from the hospital. In *Table 1* it also will be seen that the smallest infants were exclusively artificially fed. It is perhaps reasonable to assume that had we resorted to the use of breast milk more babies would have been discharged on breast milk. Granted that this would have occurred, it is indeed doubtful that breast feeding would have been long continued after discharge from the hospital. We rather suspect that the large majority of premature infants, no matter how they are fed during their hospital stay, will of necessity be dependent entirely or in part upon bottle feeding very early in their first year. If this assumption is true it is imperative that the choice of food minimize in so far as possible the dangers of bottle feeding. We know of no safer substitute for breast milk than whole lactic acid milk.

MORBIDITY AND MORTALITY

It is diffcult to compare the results in one series of premature infants with other reports on this subject. Mortality statistics are very materially influenced by factors such as age, weight, individual vitality, maternal conditions and place of birth. We would emphasize again the fact that we have included in this report every infant admitted to our nursery breathing. Since the majority of the infants were born in the hospital they arrived in the nursery a few minutes after delivery. This fact accounts in a great measure for the relatively large number of infants dying within the first twenty-four hours. A large proportion of these died within a few minutes to several hours after admission to the pediatric service. Obviously had these infants been born outside the hospital they would not have survived sufficiently long to gain admission to our nursery. If one is to compare the relative success of a particular nursery routine only those babies should be included that live as long as twenty-four hours.

Certainly no statistics concerning premature mortality are reliable that do not take into consideration the various weight groups. The tables presented in this report are arranged in this fashion and in addition we have attempted to show the effect on hospital mortality of an apparent indifference to breast feeding.

In *Table 3* are listed certain maternal conditions associated with premature delivery arranged according to weight and death of the infant. In sixty-five instances no cause for prematurity was recorded. Of the apparent causes toxemias of prengancy top the list, with twin pregnancy second in importance. It is interesting to note the apparent infrequency of syphilis as a cause of premature delivery.

In *Table 4* are recorded certain conditions of labor and delivery and the possible relation of these factors with death of the infant. The mortality rate in any series of premature infants is materially affected by obstetrical practices and procedures. We shall not attempt to draw any conclusions from this table. It is obviously unfair to compare the various obstetrical conditions one against the other, because death in the infant depends so largely

Table 3

BIRTH WEIGHT IN GRAMS

Abnormality of Pregnancy	Total	No Wgt.	Less 1000	1000 1250	1250 1500	1500 1750	1750 2000	2000 2250	2250 2500	Died	Mortality Per cent
None	140	1	2	11	6	8	11	32	69	28	20.0
Pre-eclampsia	63	1	3	2	5	6	10	19	17	13	20.6
Twin	36		5	2	2	4	6	9	8	13	36.1
Twin and pre-eclampsia	21	0	0	1	1	3	4	5	7	5	23.8
Placenta previa	16	1	0	2	2	2	3	6	0	6	37.5
Eclampsia	26	1	1	2	0	2	3	10	7	7	26.9
Acute infection	19	0	4	3	0	2	3	2	5	13	69.4
Premature separation of placenta	11	1	2	1	1	2	1	3	0	6	54.5
Vaginal bleeding	5	1	0	1	2	0	0	0	1	2	40.0
Twin and hydramnios	4	0	0	0	0	3	1	0	0	1	25.0
Twins and syphilis	4	0	0	2	0	1	1	0	0	3	75.0
Contracted pelvis	4	0	0	0	0	0	0	2	2	0	0
Exertion	3	0	1	1	1	0	0	0	0	2	66.6
Abortion	3	0	0	0	1	1	0	1	0	2	66.6
Syphilis	4	0	0	0	0	2	1	0	1	0	0
Twin and eclampsia	2	0	1	0	0	0	1	0	0	2	100.0
Premature rupture of membranes	6	0	0	0	0	0	0	1	5	1	16.6
Hyperemesis gravidarum	2	0	0	1	0	0	0	0	0	1	50.0
Placenta previa and twin	2	0	0	0	1	1	0	0	0	2	100.0
Hyperemesis, pre-eclampsia and twin	2	0	0	0	0	2	0	0	0	0	0
Twins, pre-eclampsia and syphilis	1	0	0	0	0	0	1	0	0	0	0
Placenta previa and syphilis	1	0	0	0	0	0	0	0	1	0	0
Fibroid uterus	2	0	0	0	1	0	0	0	1	1	50.0
Hydramnios and syphilis	1	0	0	0	0	0	0	1	0	1	100.0
Pre-eclampsia and congestive heart failure	1	0	0	0	0	0	0	0	1	0	0
Pyelitis and syphilis	1	0	0	0	0	0	0	1	0	0	0
Twins and hyperemesis	2	0	0	0	1	0	1	0	0	0	0
Cardiac decompensation, pneumonia and pertussis	1	0	0	0	0	0	0	1	0	0	0
Ectopic pregnancy	1	1	0	0	0	0	0	0	0	1	100.0
Heavy lifting and vaginal bleeding	1	1	0	0	0	0	0	0	0	1	100.0
Thoracoplasty	1	1	0	0	0	0	0	0	0	?	?
Epilepsy	1	1	0	0	0	0	0	0	0	?	?

on those factors responsible for premature delivery and upon the weight and vitality of the infant in question.

Cesarean section would seem in this series to have an unduly high infant mortality. It will be noted, however, that six of the infants delivered in this fashion were under 1000 grams, and three others less than 1250 grams. The successful showing of the low forceps operation may well be explained by the size and vigor of the infants delivered in this fashion.

Data pertaining to the vitality of all infants graduated from the hospital are presented in *Table 5*. It will be seen that the smaller weight brackets are well represented in this group of infants.

The first twenty-four hours exacted its usual high toll, ninety-two infants failing to survive this period. Of the 340 infants surviving the first twenty-four hours, 335 lived forty-eight hours or longer. Twenty-two and four-tenths per cent of these 432 infants died within forty-eight hours. The mortality percentage of the group of infants surviving the first forty-eight hours was 14.6.

In *Table 6*, 432 cases are arranged according to color. It is interesting to note the close mortality rate, particularly since the two groups have occupied separate nurseries.

Table 4

BIRTH WEIGHT IN GRAMS

Abnormality of Labor	Total	No Wgt.	Less 1000	1000 1250	1250 1500	1500 1750	1750 2000	2000 2250	2250 2500	Died	Mortality Per Cent
None	214	4	8	11	15	17	22	50	76	53	24.7
Breech extraction	38	1	0	3	4	8	5	5	12	12	31.5
Voorhees bag	28	0	1	3	1	5	3	7	8	10	35.7
Cesarean section	28	1	6	3	0	2	3	5	8	14	50.0
Low forceps	32	1	0	0	0	1	2	9	19	4	12.5
Version and breech extraction	12	1	0	1	1	2	3	2	2	6	50.0
Precipitate	10	0	0	3	3	0	0	2	2	6	60.0
Artificial rupture of membranes	6	0	1	2	1	0	1	1	0	3	50.0
Voorhees bag and breech extraction	4	0	0	0	1	0	2	1	0	2	50.0
Voorhees bag, version and extraction	5	1	0	0	0	0	0	3	1	1	20.0
Medical induction—low forceps	3	0	0	0	0	2	1	0	0	0	0
Locked twins	2	0	2	0	0	0	0	0	0	2	100.0
Mid forceps	1	0	0	0	0	0	0	1	0	0	0
Medical induction	1	0	0	0	0	0	0	1	0	0	0
Voorhees bag and low forceps	1	0	0	0	0	0	0	0	1	0	0
Acute inversion of uterus	1	0	0	0	0	0	1	0	0	0	0
Manual removal of placenta	1	0	0	0	0	1	0	0	0	0	0
Primary inertia	1	0	0	0	0	0	0	1	0	0	0
Voorhees bag and mid forceps	1	0	0	0	0	0	0	1	0	0	0

Table 7 gives the data concerning the vitality of 340 infants arranged according to weight groups and type of feeding. This table illus-

Table 5

VITALITY OF PREMATURE INFANTS GRADUATED

Birth Wgt. in Grams	Total Admissions	No. Surviving First 24 Hours	No. Surviving First 48 Hours	Graduated		Percent Graduated of Infants Surviving First 48 Hours
				No.	Percent	
Less than 1000	26	0	0	0	0	0
1000-1250	38	24	24	7	18.4	29.1
1250-1500	29	20	19	10	31.0	52.6
1500-1750	42	28	26	23	54.7	88.4
1750-2000	53	47	46	36	67.9	78.2
2000-2250	99	93	92	86	86.8	93.4
2250-2500	133	128	128	124	93.2	96.9
No Weight	12	0	0	0	0	0
TOTAL	432	340	335	286	66.2	85.4

Table 6

RACE MORTALITY

Race	Total	Lived	Died	Mortality Per Cent
Colored	96	66	30	31.2
White	336	220	116	34.5

Table 7

VITALITY DATA OF 340 BABIES ARRANGED ACCORDING TO WEIGHT GROUP AND TYPE OF FEEDING

Breast Milk	Number	Lived 48 Hours	Graduated	Per cent Graduated
1750-200 Gm.	3	3	2	66.6
2000-2250 Gm.	5	5	5	100.0
2250-2500 Gm.	4	4	4	100.0
TOTAL	12	12	11	91.6
Whole Boiled Milk				
1750-2000 Gm.	2	2	0	0
2000-2250 Gm.	3	3	3	100.0
2250-2500 Gm.	3	3	3	100.0
TOTAL	8	8	6	75.0
Breast Milk and Lactic Acid Milk				
1000-1250 Gm.	2	2	0	0
1250-1500 Gm.	2	2	2	100.0
1500-1750 Gm.	8	8	8	100.0
1750-2000 Gm.	14	14	13	92.8
2000-2250 Gm.	54	54	52	96.2
2000-2250 Gm.	105	105	104	99.0
TOTAL	185	185	179	96.7
Lactic Acid Milk				
1000-1250 Gm.	22	22	7	31.8
1250-1500 Gm.	18	17	8	44.4
1500-1750 Gm.	20	18	16	80.0
1750-2000 Gm.	29	28	21	72.4
2000-2250 Gm.	30	29	25	83.3
2250-2500 Gm.	16	16	13	81.2
TOTAL	135	130	90	66.6

Table 8

Chart No.	Birth Wt.	Death Wt.	Length Life	Day Birth Wt. Regained	Obvious Cause Death	Possible Cause of death	Postmortem	Remarks
83002	1265	1100	4	No		Congenital weakness		Very unstable temperature
52091	1300	1090	12	No		Diarrhea unqualified		
88889	1315	1160	4	No		Congenital weakness	None	Temperature very unstable Almost constant cyanosis
92217	1315	1310	5	No	Hemorrhagic disease of new born		None	Prolonged Rodda. Cyanosis with vomiting of blood and feedings
113806	1330	2960	84	7	Severe weakness		Marked jaundice Enlarged spleen	Gradually increasing jaundice
99121	1375	1220	14	No	Bilateral bronchopneumonia		None	Doing well until onset of pneumonia
111138	1380	?	2	No		Congenital weakness	None	Cyanosis
104841	1405	1275	7	No	Cerebral hemorrhage. Atelectasis		Bilateral hemorrhage into thalamus and lateral ventricles. Atelectasis	Frequent cyanosis
75148	1495	1310	17	No		Diarrhea unqualified	None	
106751	1530	Not Weighed	31 hrs.	No	Atelectasis		None	Condition poor from birth
75147	1570	1245	12	No	Pneumonia	Diarrhea unqualified	Stomach contents aspirated into lungs. Congestion large intestine	Vomited at intervals
110588	1665	1460	22	No	Asphyxia		None	Aspirated regurgitated food
84162	1710	1700	33	24		Congenital weakness	Hypostatic congestion lungs. Congestion of mucosa of stomach	Unstable temperature Irregular weight gains
83742	1770	1470	17	No	Atelectasis		None	Cyanosis frequent Respiratory difficulty
81827	1790	1490	14	No		Diarrhea unqualified	Malnutrition. Congestion of G. I. tract. Multiple areas atelectasis	Blood in stools
112106	1795	1720	22	11	Pneumonia		None	Cyanosis; respiratory difficulty
51472	1025	?	12	?		Congenital weakness		9 days old on admission. Poor care before admission. Unstable temperature

Table 8 (Continued)

Chart No.	Birth Wt.	Death Wt.	Length Life	Day Birth Wt. Regained	Obvious Cause Death	Possible Cause of Death	Postmortem	Remarks
112218	1045	880	10	No	Atelectasis Pneumonia		None	Frequent cyanosis
124995	1060	840	16	No		Congenital weakness	No abnormal findings	Admitted on fourth day. No care at home and no food given.
66335	1065	2005	77	13	Nasal Diphtheria. Empyema. Asphyxia	Congenital syphilis	Congenital syphilis. Empyema (bilateral). Abscesses thoracic wall. Congestion in lungs	
81183	1080	1100	32	?		Congenital weakness	None	3 weeks old when admitted. Poor care at home. Vomited. Unstable temperature
72417	1100	1060	22	11		Diarrhea unqualified		Temperature unstable. Vomited frequently
104339	1105	1320	38	19		Diarrhea unqualified	None	Gained despite diarrhea. No cause for respiratory failure
110151	1115	1400	34	16		Diarrhea unqualified	None	Blood in stools. Temperature unstable
63035	1125	1015	29	No	Pyelitis		None	3 weeks old when admitted.
74100	1140	1090	34	No		Diarrhea unqualified	None	Doing well until onset of diarrhea. 3 days old on admission
66336	1145	2075	87	13	Nasal diphtheria; cervical abscess; pneumonia	Congenital syphilis	Congenital syphilis. Pneumonia. Nasal diphtheria. Cervical abscess.	
120206	1150	905	7	No		Congenital weakness	Congestion of cerebral vessels	Very unstable temperature. Frequent cyanosis
83003	1160	1000	7	No		Congenital weakness		Very unstable temperature. Failure to gain
86232	1195	1045	6	No		Congenital weakness		Unstable temperature. Repeated cyanosis
110134	1235	1000	13	No	Atelectasis		Atelectasis	Frequent cyanosis
66672	1260	1965	47	7	Intestinal obstruction		Congenital anomaly of cecum	Died 2 hours following operation
90609	1800	1730	4	No		Congenital weakness	None	Cyanosis. Marked discoloration of body when admitted
111426	1845	1755	2	No	Cerebral hemorrhage; atelectasis	Congenital weakness	Hemorrhage in caudate nucleus and under meninges. Atelectasis	Cyanosis
96727	1855	1885	22	12		Diarrhea unqualified	None	Doing well until diarrhea began. Blood in stools
89807	1860	1930	38	?		Diarrhea unqualified	None	Brought in when two weeks old. Had been on L.A.M.

Table 8 (Concluded)

Chart No.	Birth Wt.	Death Wt.	Length Life	Day Birth Wt. Regained	Obvious Cause Death	Possible Cause of death	Postmortem	Remarks
91923	1870	1520	13	No		Congenital weakness	Emaciated. Congested at base of right lung. Congestion arachnoid	Failure to gain weight. Cyanosis. Respiratory failure
104478	2000	1965	2	No		Congenital weakness	None	Unstable temperature. Cyanosis. Cheyne-Stokes respiration
98825	2110	1700	14	No	Bronchopneumonia		None	Very unstable temperature throughout
111419	2140	2055	18	No	Lobular pneumonia		Lobular pneumonia	
110850	2180	1640	14	No		Congenital weakness	None	Cyanosis. Respiratory difficulty. Vomited at times
82534	2160	2080	30	17		Diarrhea unqualified	None	Took feedings poorly throughout
118214	2195	1815	6	No	Lobular pneumonia; congenital heart		Patent ductus arteriosus. Lobular pneumonia. Congenital hypertrophy of heart.	Cyanosis. Respiratory difficulty
89621	2265	1980	15	No		Congenital weakness	None	Very unstable temperature. Failure to gain weight
116641	2295	1915	3	No	Congenital heart; atelectasis		Patent ductus arteriosus and foramen ovale	Frequent cyanosis

trates in a striking fashion how easy it is to arrive at false conclusions from statistical studies.

On the 185 infants fed breast milk complemented with whole lactic acid milk, 96.7 per cent were graduated from the hospital. On the other hand, of the 135 infants fed exclusively on whole lactic acid milk 66.8 per cent were graduated. Can the difference in mortality of the two groups be used as an argument against the use of artificial feeding? We do not feel that this is a justifiable conclusion. Attention should be called to the fact that all of the infants receiving variable amounts of breast milk were born in the hospital. Furthermore, they were with few exceptions sufficiently vigorous to nurse their mothers. We would again call attention to the small amount of breast milk that these infants actually received, and that a very large proportion were being fed entirely on lactic acid milk by the time of graduation from the hospital.

A study of the apparent or probable causes of death in the cases of the forty-four infants fed exclusively on lactic acid milk does not point to the type of feeding as the probable explanation of death in many instances. Short protocols giving the essential facts in these cases are listed in *Table 8*, and *Table 9* contains a summary of the obvious and possible causes of death.

These findings do not suggest any lack of resistance on the part of these infants deprived of breast milk. The fifteen infants classified as congenitally weak appeared to possess too little vitality for the maintenance of a separate existence, and certainly death could not be ascribed to the type of feeding.

Table 10 gives our mortality as related to place of birth. Our experience substantiates the well known fact that premature infants born outside a hospital have less chance of survival. Three hundred and ninety-six of the infants described in this report were born in the hospital and thirty-five outside. 62.8 per cent of those born outside died as compared to a mortality of 31.3 per cent for those born inside.

Mortality of those surviving 24 hours and born in hospital is 12.5 per cent, and those born outside hospital is 51.8.

Of the babies born inside and surviving twenty-four hours, 12.5 per cent subsequently died as compared to 51.8 per cent for those born outside and surviving the first twenty-four hours of life. The thermal shock associated with out-

Table 9

OBVIOUS AND POSSIBLE CAUSE OF DEATH IN FORTY-FIVE PREMATURE INFANTS FED EXCLUSIVELY ON LACTIC ACID MILK*

Obvious Cause	No. Cases
Pneumonia	4
Pneumonia and diarrhea	1
Pneumonia and atelectasis	1
Pneumonia and congenital heart	1
Nasal diphtheria and empyema	1
Nasal diphtheria, pneumonia and cervical abscess	1
Congenital intestinal obstruction	1
Hemorrhagic disease	1
Congenital heart disease	1
Cerebral hemorrhage and atelectasis	2
Severe jaundice (obstructive)	1
Asphyxia (aspiration of food)	1
Pyelitis (21 days old on admission)	1
Diarrhea (14 days old on admission)	1
Total	18

Possible Cause	No. Cases
Diarrhea (unqualified)	9
Atelectasis	3
Congenital weakness	15
(All cases were, in general, characterized by cyanosis and unstable temperatures.)	
1 case 4 days old on admission	
1 case 9 days old on admission	
1 case 21 days old on admission	
(All had very poor care outside.)	
Total	27

*Of the forty-five cases dying, twenty-five were under 1,500 grams at birth, six of these ranging between 1,000 and 1,100 grams, and eight between 1,100 and 1,200 grams.

Table 10

MORTALITY AS RELATED TO PLACE OF BIRTH AND ARRANGED ACCORDING TO WEIGHT GROUPS

Birth Weight in Grams	Born in Hospital	Died	Mortality Percentage	Born Outside	Died	Mortality Percentage
Less 1000	24	24	100	2	2	100
1000-1250	24	19	79.2	14	12	85.7
1250-1500	23	17	73.4	6	2	33.3
1500-1750	40	19	47.5	2	0	0
1750-2000	47	12	25.2	7	5	71.4
2000-2250	97	13	10.2	1	0	0
2250-2500	30	9	6.9	2	0	0
No weight	11	11	100	1	1	100
Total	396	124	31.3	35	22	62.8

side birth appears to confer a more lasting damage.

Table 11 lists the more important necropsy findings in the cases of forty-two infants.

Ninety-two of the infants here reported died within the first twenty-four hours, a large proportion being obviously non-viable. To what extent death might have been avoided by better physical equipment in the nursery is problematical. It is unlikely that these early deaths would have been very materially lessened by such physical measures. In most instances we were able to control thermal shock reasonably well by the somewhat homely methods previously described. In *Table 12* are recorded the twenty-four hour deaths arranged according to weight groups.

It seems unlikely that further improvement in treatment, and physical conditions in the nursery will materially reduce the premature mortality rate. Further advances must come from the prevention of those causes responsible for premature delivery and improvement in obstetrical diagnosis and procedures.

Table 11

NECROPSY FINDINGS

Chart No.	Postmortem Findings
96652	Cerebral hemorrhage
96541	Hemothorax; hemoperitoneum
92815	Atelectasis
117725	Atelectasis; hemangioma of mitral valve
118558	Patent foramen ovale and ductus arteriosus; atelectasis
108627	Hemothorax; atelectasis
118032	Atelectasis; cerebral hemorrhage
74942	Patent foramen ovale
82157	Patent foramen ovale; atelectasis
75827	Enlarged thymus
86875	Cerebral hemorrhage; hemoperitoneum
94875	Cerebral hemorrhage
114086	Acute suppurative thymitis; pneumonia
118559	Patent foramen ovale, ductus arteriosus and venosis; contusion of liver; atelectasis
67230	Patent foramen ovale; cerebral hemorrhage
51002	Congenital syphilis; atelectasis
71225	Patent foramen ovale
73785	Patent foramen ovale; atelectasis
75201	Cerebral hemorrhage
47217	Cerebral hemorrhage
91912	Atelectasis
88757	Atelectasis; patent foramen ovale
94405	Atelectasis
105521	Atelectasis
106981	Atelectasis
102022	Atelectasis
114611	Atelectasis
81637	Atelectasis
50163	Atelectasis
11426	Pneumonia; congenital syphilis
111419	Pneumonia
110134	Atelectasis
116641	Patent foramen ovale and ductus arteriosus; atelectasis
113806	Enlarged liver; marked jaundice
118214	Patent ductus arteriosus; pneumonia
66335	Nasal diphtheria; empyema; abscesses of thoracic wall; congestion of lungs; congenital syphilis
66336	Nasal diphtheria; cervical abscess; congenital syphilis; pneumonia
66672	Congenital anomaly of cecum; intestinal obstruction
81827	Gastro-enteritis
84612	Pneumonia
91923	Congestion of arachnoid; atelectasis
104841	Atelectasis; cerebral hemorrhage
75147	Gastro-enteritis
89377	Patent foramen ovale

Table 12

WEIGHT GROUP OF THOSE LIVING 24 HOURS OR LESS

Birth Weight in Grams	No. of Cases
Less 1000 grams	26
1000 to 1250 grams	14
1250 to 1500 grams	9
1500 to 1750 grams	14
1750 to 2000 grams	6
2000 to 2250 grams	6
2250 to 2500 grams	5
No weight grams	12
Total	92

DISCUSSION

Published reports over a period of fifteen years concerning premature infants in this country show a mortality ranging from 18 to 77 per cent. It is difficult to interpret this apparent disparity in results. In many instances nursery routine, methods of feeding, and nursery equipment seem strikingly similar, yet results are vastly different. Postnatal care in such instances would not seem to be the answer, but rather the vitality of the groups in question, this in turn being very materially affected by maternal conditions, social and economic status, obstetrical procedures and practices, as well as place of birth.

It is difficult to evaluate in their order of importance the various factors which make for success in the management of premature infants. Perhaps they should be arranged in this fashion: (1) An intelligent, enthusiastic and conscientious nursing staff and an attending staff that is premature-minded, (2) measures for prevention of thermal shock, (3) methods of feeding, (4) prevention of infection, and (5) physical equipment in the nursery.

In recent years the more comprehensive reports concerning the care of premature infants have come from institutions which can well boast of very elaborate arrangements for the reception of babies born prematurely. They describe nurseries in which temperature and humidity are automatically kept at a certain figure, and which are staffed by graduate nurses specially trained for this purpose. The necessary supply of breast milk is apparently available either from wet nurses or procured at a fancy price from breast milk stations. These reports are most helpful and instructive, but tend to be of small comfort to the average small hospital and many a large one amply blessed with clinical material but with a budget already strained to the breaking point. With this thought in mind we venture this report and have described briefly our most inadequate nursery arrangements. We are unwilling to admit that costly mechanical nursery devices will in any large measure solve the problem of the premature infant and venture the opinion that the improved mortality rate to be derived from such arrangement is in part but the expression of increased enthusiasm of a staff that has become more premature-minded. This statement will seem less ungraceful because of the fact that since this paper was begun our newly-borns have been provided with ample nursery space all of which is mechanically conditioned. It is hoped that this improvement in facilities will be expressed in our results, particularly in the lower weight brackets.

In our enthusiasm for whole lactic acid milk as a food for premature infants we are not unmindful of the potential dangers associated with artificial feeding. It is our belief that irrespective of the type of feeding employed in the early weeks the large majority of premature infants will be dependent entirely or in part upon artificial food very early in the first year of life. If this is true the choice of food becomes a factor of great importance. With this thought in mind we have recorded our experience with whole lactic acid milk and suggest the wider use of this type of feeding in those cases in which a substitute for breast feeding would seem necessary.

DISCUSSION (*Abstract*)

Dr. Angus McBryde, Durham, N. C.—The only method by which we can accurately compare statistics on premature mortality is to include all those infants who breathe after birth. It also is necessary to compute the mortality on basis of birth weight. The mortality rate may be greatly improved by including in the series a large number of infants weighing more than 2,000 gm.

There are two main methods of attack in reducing premature mortality, better prenatal and natal care and better postnatal care of those infants that weigh less than 1,800 gm. at birth. Gengenbach has reported very low infant mortality rates in those mothers who regularly were seen by a physician as compared to the mothers who paid few or no visits to the physician. Clifford has demonstrated the importance of accurately determining the age of the fetus by means of the x-ray. He has stressed the necessity of continuing pregnancy for one or two weeks, thus securing a viable infant in borderline cases. Also, in other instances, such as mothers with heart disease, it is necessary to interrupt the pregnancy earlier to secure a viable infant.

The greatest premature mortality is in the lower weight ranges, below 1,800 gm. In the lower weight

ranges, it is not necessary to have elaborate apparatus for regulation of temperature and humidity in order to lower the death rate. During the winter months the temperature usually can be kept constant and the humidity can be kept high by using usual means of increasing the room humidity. During the summer months, especially in the South, the temperature tends to rise and so does humidity, so that some means of regulating these factors, such as the less elaborate air-conditioning unit, must be used. As Dr. Waddell has said, it is most important to let the premature infant alone as much as possible and that some one of the pediatric staff be primarily interested in the care of premature infants.

Dr. Amos Christie, Baltimore, Md.—Papers such as we have just heard are particularly timely when we consider the tremendous part which death from prematurity plays in our infant mortality rate. Approximately 50 per cent of deaths of infants under one day of age are due to prematurity.

It will be noted that the mortality in Dr. Waddell's premature group for those born in the hospital was 31 per cent. This compares favorably with the 25 per cent mortality which should be expected in this group. However, there is a 62 per cent mortality in the group born outside and brought to the hospital. This is much too high and although it is an experience shared by all of us, the Chicago figures of Dr. Hess which show a 34 per cent mortality in a similar group, furnish an example of what can be done by the development of such details as heated premature ambulances and a city-wide premature consciousness second to none in this country. Dr. Waddell's statistics show the white mortality to be higher than the mortality in the colored premature infants. This is to be expected and exists in all premature studies. He has also noted that the mortality is higher in the male than in the female premature infants. This is also a consistent finding in premature studies, and together with the racial difference, is probably explained on the basis of relative maturity at birth.

I concur in what Dr. Waddell has said about the lack of need for fancy and expensive rooms and equipment for the care of the premature infant; but, whether it be due to this equipment or whether it creates in a staff a feeling of prematurity-consciousness, the mortality with such equipment is undoubtedly lower than in premature nurseries without such equipment.

Still another point which will bear a word of warning is the feeding of the premature. Granted that with our newer knowledge of infant feeding, artificial formulae are safe and lactic acid evaporated milk is one of the safest, the fact remains that whether one analyzes his results statistically or purely by clinical impression, there has never been improvised a better feeding than that heritage given to most mothers, that is, breast milk. The main value of breast milk in the feeding of the premature as I see it, is the impossibility of overfeeding. You will note Dr. Waddell's mortality from diarrhea. It is 25 per cent, and this evidence of indigestion may have been partially prevented by a lower caloric feeding. In conclusion, I believe that artificial feeding can be safely done in a premature group, but I also believe that the further down in the economic scale our feeding groups are, the more need there is for breast feeding.

INTESTINAL PARASITIC INFECTIONS COMPLICATING PREGNANCY*

By E. L. KING, M.D.
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and
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In 1929 one of us,[1] in a paper on hookworm disease complicating pregnancy, reported that 12, or 6.7 per cent, of 180 patients admitted to the white obstetrical service of the New Orleans Charity Hospital were found to be harboring this infection. These patients represented the admissions of a few months. A more comprehensive survey was decided upon, which would include other parasitic infections as well. During the past 6½ years, stool examinations have been made on 3,290 white obstetrical patients; in some instances, two or three specimens from the same patient have been studied, so that a total of over 5,000 careful examinations have been made. The results are tabulated as follows:

INTESTINAL PARASITES IN NEW ORLEANS

Total number of cases examined from April, 1930, through September, 1936.....3,290

	Positive Findings	Percentage of Total
Endameba histolytica	320	10
Giardia lamblia	165	5
Necator americanus	185	5.6
Trichocephalus	135	4
Enterobius vermicularis	24	0.7
Ascaris	115	3.5
Taenia saginata	3	0.09
Hymenolepis nana	11	0.33

Thus it will be seen that these various parasitic infections are fairly common in the type of white patients treated in a Southern charity hospital. It is to be noted that the women were admitted as obstetrical patients, and did not seek treatment for the parasitic infection, the presence of which, in the large majority of instances, was not suspected by the patients. In approximately 50 per cent of women, multiple infections were discovered. The importance of such findings from a public health standpoint is obvious, as these individuals, in addition to be-

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ing infected themselves, are potential sources of infection to others. The women were from both rural and urban areas, in the ratio of 55 per cent rural and 45 per cent urban. If they had been subdivided into these two groups, the percentages would have been found to be higher in the rural group, because of the unsatisfactory hygienic conditions of their environments.

In considering the various types of parasitic infections in detail, it is seen that the most important ones in this series are *Endamoeba histolytica* (320, or 10 per cent of the total), hookworm (185, or 5.6 per cent of the total) and ascaris (115, or 3.5 per cent of the total). The other parasites found are either of no pathological significance (giardia, enterobius and trichocephalus) or were found so seldom (taenia, hymenolepis) as to be of little importance. A brief consideration of the three chief offenders may be of interest.

As noted in the table, *Endamoeba histolytica* was found in 320 patients. This figure was obtained from the examination of one to three stools from each patient, which is universally admitted to be inadequate for a proper survey. Parasitologists prefer to examine at least six specimens before definitely concluding that this parasite is not present. It was not feasible to conduct such a study on these patients, as the majority were in the hospital for a short period of time; had they been thoroughly studied, there is no doubt that a much higher incidence would have been found. Craig[2] reported that 12.7 per cent of 189 physician students of the Army Medical School in Washington harbored this parasite. Faust[3] found that 8.27 per cent of medical students and 9.05 per cent of private patients (in New Orleans) were infected, and that the figures for the male and female medical wards in the New Orleans Charity Hospital were 27.2 per cent and 13.1 per cent, respectively. Craig[2] stated that a conservative estimate would be that between 5 and 10 per cent of the population of the United States harbor *Endamoeba histolytica;* that is, between six and ten million individuals. This authority is thoroughly convinced that there is no infection with this parasite without the production of pathologic lesions, minute and symptomless in many instances, but capable of developing clinical manifestations under proper conditions. Contamination of food by handlers is the chief source of infection; at times the water supply is responsible, especially in rural districts, where the water may not be adequately protected from fecal pollution. Craig[4] feels that it is essential that every known case of infection be properly treated. He stresses the point that carriers who are practically symptom free (without diarrhea or dysentery) pass the encysted forms which can infect other individuals, while patients with loose stools discharge chiefly the motile forms, which are non-infectious.

From an obstetrcial point of view, it is apparent that clinical amebiasis, especially if severe, might prove to be a serious complication. None of our patients presented serious symptoms, though in approximately one-half of them the presence of diarrhea or dysentery of variable intensity was noted in the records. We agree with Craig that all individuals with amebic infection should be treated, and see no objection to, and many reasons for, the treatment of pregnant women so infected. We know that their general health would be improved, and would not expect the occurrence of abortion or of premature labor as a result of the treatment. However, we were not able to treat many of our patients, due to the fact that the large majority were in the ward for only a few days. It might be noted that the drugs most favored in the management of this condition are chinioform, carbarsone and vioform. Time does not permit the discussion of the details of treatment with these agents.

Hookworm infection was found in 185 patients, or 5.6 per cent. This corresponds fairly closely with the 6.7 per cent incidence noted by King[1] in the preliminary survey. This condition, too, is a common one, and we feel that for several years its importance as a public health problem has been considerably underestimated. Twenty-five or more years ago, a great hue and cry was raised about hookworm disease, and mass campaigns were conducted, one of the most important being that of the Rockefeller Sanitary Commission in Mississippi. These campaigns were productive of great improvement in the localities involved, but did not by any means eradicate the infection in such areas. Thus Keller, Leathers and Ricks,[5] in 1934, upon examining 44,380 stool specimens from white persons in 52 counties of Mississippi, found 19.6 per cent to be infected. In 6,441 specimens from Negroes in 32 counties, the rate was 1.4 per cent. The authors state that it is well known that hookworm infection in Negroes in the Southern states is relatively unimportant. This is probably due to an acquired racial immunity. The figures of these investigators, when compared with those of the Rockefeller Sanitary

Commission, compiled in the same State in 1910-14, show a vast improvement over the conditions found by the Commission. However, when we note that these investigators estimate that there are approximately 86,000 infected persons in the countries studied, we see that there is still a hookworm problem. Similar conditions naturally exist in the other Southern states.

Coming now to the obstetrical side of this problem, it is apparent that a woman suffering from this disease is handicapped to a degree corresponding to the intensity of the infection. This is due in a great part to the anemia commonly found, with the concomitant lowering of resistance. Wickramasuriya,[6] writing from Ceylon (1935), is particularly pessimistic, stating that hookworm disease as a complication of pregnancy is more serious than syphilis, eclampsia, or sepsis. He reports that in the Soysa Lying-In Hospital (Ceylon), in the years 1932 and 1933, there were 74 deaths due to hookworm in approximately 11,000 admissions. These, however, were poverty-stricken individuals of the lowest strata, from heavily infected regions. The increased incidence of toxemia of pregnancy (including eclampsia), was noted by this writer, also by Rowan in Mississippi,[7] Tuberville in Florida,[8] and Opocher[9] in Italy. King[1] felt that the development of this condition was favored by the occurrence of anemia, and noted that 8 of the 9 cases of toxemia in his series were found in patients with severe anemia. Fetal death, abortion and premature labor have been reported in association with severe infections, especially by this writer from Ceylon. Perkins[10] also stresses these various possibilities in obstetrical patients with complicating hookworm infection. In the present series, we found a few patients with marked anemia, and none with severe toxemia. Many of them could be classed as carriers, as they were symptomless, with mild infections. We feel that all such patients should be treated more than once if possible (in order thoroughly to eradicate the infection), and many of our patients were treated as adequately as possible. We have had no case of abortion or premature labor as a result of the treatment, and feel that, on the contrary, such a termination is often avoided because of the improved condition of the patient following the eradication of the infection. We prefer the use of tetrachlorethylene in 3 c. c. doses given in hard gelatin capsules on an empty stomach; a saline purge is given the night before, and again two hours after the administration of the above drug. If ascaris is also present, hexylresorcinol is given at the same time. As noted by Rhoads *et al*,[11] it is as necessary to treat the anemia as to eradicate the infection, and obivously this is particularly true in pregnancy.

The third parasitic infection under consideration, ascariasis (115 cases, or 3.5 per cent), is also of considerable general importance. Keller,[12] in a report of an investigation made in Tennessee, states that he found an infection incidence of 27.6 per cent in 31,999 individuals from 71 countries. It was notably highest in children between 5 and 9 years of age (36.1 per cent). This infection, however, produces little general disturbance unless the worms migrate into dangerous areas (such as the appendix or the common bile duct) and hence it is not as a rule a serious complication of pregnancy. Of course, mild or severe conditions may develop, such as nausea and vomiting, intestinal discomfort, intestinal obstruction, or perforation of the gut and peritonitis. Treatment is of course indicated, in the pregnant as in the non-pregnant, and interruption of the pregnancy is not produced. The most efficacious method is the administration of 1 gram of hexylresorcinol crystals in hard gelatin capsules, given in the morning on an empty stomach, and followed by a saline purge, with no food for five hours after the drug is taken.

In this brief review we have attempted to emphasize the frequency of these parasitic infections, especially in the territory in which the members of this Association are practicing. It is particularly important to call the attention of rural practitioners to the prevalence of these infections and to their occurrence as complications of pregnancy. We wish to emphasize the importance of routine stool examinations in the study of patients, pregnant and non-pregnant. Finally, we wish to lay stress upon the necessity of treatment where one (or more) of these infections is found in a pregnant woman, and to allay any fears regarding the possibility of causing abortion or premature labor by such treatment.

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DISCUSSION (*Abstract*)

Dr. Nicholson J. Eastman, Baltimore, Md.—From an obstetrical viewpoint, the importance of any incidental disease complicating pregnancy is closely related with two circumstances: first, do pregnancy, labor and the puerperium affect the course and prognosis of the intercurrent disease; and second, does the intercurrent disease affect the course of pregnancy, labor and the puerperium? As far as I am aware, there is no evidence to show that the course and prognosis of intestinal parasitical infestations are affected in any way by pregnancy. On the other hand, there is ample evidence to indicate that intestinal parasites may have important effects on the course of pregnancy and the puerperium. For instance, the anemia which is commonly seen in hookworm may in a pregnant woman simulate closely the hypochromic microcytic anemia which we now see in a large proportion of our obstetrical patients. Physicians who practice south of the northern border of North Carolina may well look upon hookworm as a possible cause of certain anemias of pregnancy and should take appropriate steps to rule out or treat this condition as the case may be. Again, hookworm may be the cause of inadequate lactation and should be considered as a possible cause of nursing difficulties in the areas mentioned.

I should like to utter a word of caution against performing operations, obstetrical or otherwise, on patients with ascariasis. These worms, as is well known, have a tendency to migrate and when the posterior pharyngeal reflexes have been abolished by a general anesthetic they may crawl up the esophagus and find their way into the trachea. I have known this to constitute a serious complication of anesthesia in more than one instance, and at the Peiping Union Medical College, where many of our patients harbored ascaris, it was a rule that they should never be given a general anesthetic unless this condition had been cured. Furthermore, during the postoperative period, ascaris worms may produce a picture almost identical with that of postoperative obstruction, and I remember an instance of a patient who was about to be explored for a postoperative obstruction, when she vomited a large quantity of ascaris worms and her symptoms disappeared. In another case, the ascaris worms entered and plugged a drainage tube left after a gynecological operation. These are important practical points to bear in mind when planning operations on patients with ascariasis.

Dr. Alan F. Guttmacher, Baltimore, Md.—In the paper under discussion, the authors make no specific mention of an increase in abortion, premature labor or fetal mortality in their series. The absence of such a reference probably implies that the fetus was unaffected. The literature from both clinical and experimental angles contains many interesting reports of prenatal infection of the fetus with parasitic intestinal worms of the mother. Howard, of the International Health Board, reported a case of prenatal hookworm infestation (in British Guinea). The mother, a Negress, who had had eight living children, presented clinically the usual symptoms of hookworm disease. The child appeared normal at birth, but during the examination of the child's stool on the fourteenth day of life, many hookworm ova were found. Repeated examinations of the stool during the next few days confirmed these findings. Since it requires a minimum of four weeks for the ova to appear in the stool after infection, it is very likely that the case reported was one of intrauterine infestation. Similar cases were described by De Langen, but unfortunately his report was not available to me. Experimentally, Foster (of the Gorgas Laboratory in Panama and the Johns Hopkins School of Hygiene) has infected dog fetuses *in utero* with hookworm. In these experiments thousands of larvae were either given to the mother dog parenterally or inoculated subcutaneously when gestation was half over. Thirty-two of the thirty-four puppies born to these mothers showed ova in their stools and at autopsy showed worms in the intestinal tract.

It is interesting to pause and speculate as to the modus operandi of spontaneous hookworm infection of a fetus. We must assume that during pregnancy the mother received a cutaneous infection with hookworm larvae. According to the studies of Looss and others, such larvae first gain access to the lymphatic system of the host and then by way of the thoracic duct enter the blood stream. From this they enter the heart and then the infective larvae are scattered through the body by means of both arterial and venous blood. They are transported to the pelvic vessels and find their way into the intervillous spaces. The thin fetal ectoderm and loose connective tissue of the villus offer no effectual barrier to infection by such vigorously migratory organisms. After gaining the fetal circulation they are carried to the body of the fetus by means of the umbilical veins and thence to the right side of the heart. They reach the fetal lungs by means of the pulmonary arteries and invade and climb up the bronchial tree. From the pharynx they enter the alimentary canal of the fetus. It is obvious from this that the intestinal tract of the fetus must have reached a stage in development fitting for the reception of the infective larvae. In the human this probably could not be earlier than the fourth month.

In the brilliant report on hookworm and pregnancy as seen in Ceylon by Wickramasuriya, we find that 23 per cent of the stillbirths occurring in the De Soysa Lying-In Home were due to hookworm infection. Furthermore, many abortions and neonatal deaths were from the same cause so that in all the greatest menace to the infant before and after birth was hookworm. Unfortunately there is no report in his paper of autopsies on these antenatal and neonatal deaths, so that it is uncertain as to whether they were caused by the anemia and toxicity of the mother or actual infestation of the fetus through the placenta.

Prenatal infections by other intestinal parasites have been reported. Many observers have reported the experimental infection of dog fetuses with ascaria. Cort, one of the great American authorities in this field, says that in view of the life cycle of both ascaris and echino-

coccus it is highly likely that infection of the human fetus occasionally takes place with them.

To us obstetricians, then, these parasitic infections are not only interesting because of the effect which they have upon the mother, but also upon the fetus which she carries. It is likely that fetal infection could not be successfully treated by drugs taken by the mother since the local effect of the drug on the parasite in the intestine of the host very often is the one which destroys it.

There is another point in regard to this topic which I think should be mentioned, that is, the effect of parasitic infections of this order on fertility. Unfortunately, the literature contains practically no reference to this interesting part of the problem. We do find, however, that heavy infestations of hookworm sometimes cause amenorrhea and menstrual irregularity, and after the disease is cured the regularity of the menses is restored. In the International Health Report of 1918, we find the statement that whenever treatment of hookworm is given over large areas, the birth rate is stimulated to a marked degree. Many women become pregnant who have not borne children for years. It would be interesting to know whether this sterility is due altogether to menstrual abnormalities or if it is sometimes due to either the fertilization or implantation mechanisms' going awry. This phase of the problem could easily be attacked in the laboratory.

EMERGENCY SURGERY OF THE STOMACH AND DUODENUM*

By J. SHELTON HORSLEY, M.D.
Richmond, Virginia

Acute conditions of the abdomen often require careful consideration in making a diagnosis unless there is an external penetrating wound or some obvious lesion. A diagnostic error which results in an unnecessary operation may be of the gravest consequence.

Coronary thrombosis sometimes simulates a ruptured peptic ulcer or pancreatitis or acute cholecystitis. Opening the abdomen with such a serious cardiac lesion present may put upon the patient a burden greater than he can bear. The facts that coronary thrombosis is usually accompanied by a high leukocyte count, and that the pain may bring shock and be referred chiefly to the abdomen, demand the most careful examination and the best surgical and medical judgment to differentiate the condition. An electrocardiogram in the early stage of coronary thrombosis is not helpful, for this disease does not often show the characteristics of coronary thrombosis in the electrocardiogram until about two days after the first clinical symptoms.

A pulmonary or pleural lesion may also confuse the diagnosis of acute abdominal conditions. Capps[1] has pointed out that the sensory distribution of the phrenic nerve in the upper surface of the diaphragm is quite definite. In the outer portion of the diaphragm irritation as from pleurisy will produce pain and muscle spasm in the upper part of the abdomen. Irritation of the central part of the diaphragm near the heart causes pain to the shoulder and the root of the neck. Pneumonia accompanied by pleurisy, especially in children, is a fertile field for error in the diagnosis of lesions that appear to be in the abdomen.

Extra-gastric abdominal causes of acute abdominal conditions simulating a gastric or duodenal lesion may be cholecystitis, appendicitis, and pancreatitis. While the inflamed appendix in its normal location usually does not cause much diagnostic doubt, a high appendix beneath the liver or in a non-descent of the cecum may be a source of much puzzlement. The gallbladder occasionally ruptures, and an acute pancreatitis is often difficult to differentiate from a ruptured peptic ulcer. In appendicitis or probably in acute cholecystitis an abdominal operation is usually necessary. Operation in acute pancreatitis may not be beneficial, but it will certainly not be as harmful as in cardiac or pulmonary disease. An external penetrating wound is obvious, but there may be serious trauma to the stomach or duodenum by a blow or crushing force that leaves little if any external sign of injury.

In some cases of perforating peptic ulcer, which is one of the common causes of emergency surgery of the stomach and duodenum, there have been no previous symptoms of an ulcer, though usually a careful history will elicit former symptoms of slight gastric disturbances, and not infrequently the typical hunger pains relieved by soda, food, or vomiting. If such a history can be obtained it is quite helpful, but the absence of this history does not by any means exclude the presence of a perforated peptic ulcer. Roentgenologic examination by a flat plate which will show gas under the diaphragm is a great aid in diagnosis if it can be taken quickly and without too much manipulation.

A peptic ulcer is sometimes discovered postmortem when it apparently gave no clinical symptoms; so perforation in the absence of a history of stomach trouble may mean either that

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the ulcer has existed for some time and has not given symptoms or that the ulcer has just formed.

Another lesion of the stomach and duodenum that may call for emergency surgery is obstruction at the terminal duodenum. While this is not an infrequent condition, it is rarely thought of as causing an acute emergency. Several years ago (1928) I had a patient, a thin woman 60 years of age, who was admitted to the hospital with constant vomiting, without distention, and in extreme collapse. We gave dextrose intravenously and she improved for a while, but she died after eighteen hours. At necropsy there was obstruction of the terminal duodenum and the first part of the jejunum caused by the pressure of the transverse mesocolon. A partial obstruction had doubtless existed for a long time, but something made it complete. The absence of distention and the constant vomiting might result from an extra-gastric lesion, as nephritis or brain tumor, and this was confusing. Doubtless an early diagnosis and prompt operation would have saved this patient's life.

In stab or bullet wounds injury to the stomach or duodenum is suggested by the location of the wound. If it is probable that the stomach or duodenum has been perforated, operation should be performed as soon as possible. The operation consists in checking the bleeding and in suturing the perforations.

B. C. Willis[2] has shown that perforation of the stomach or bowel by shot may be treated satisfactorily by the expectant method. Shot, particularly birdshot, penetrating the stomach or intestine usually leave a very small wound plugged by the mucosa, often an effective closure. If an operation is done when there are many shot wounds to be treated, shock may follow and the patient will not infrequently be in a worse condition than if he had been treated conservatively, using morphine freely and resting the gastro-intestinal tract.

Trauma from an indirect injury, such as not infrequently occurs in automobile accidents in which the stomach may rupture from a quick impact of the steering wheel against the abdomen or from the person's being hurtled from the automobile, requires care both in diagnosis and treatment. If it appears that the stomach or duodenum is ruptured, operation should, of course, be done at once.

In any operation on the stomach or duodenum that may be prolonged or accompanied by shock or bleeding, intravenous injection of 5 per cent dextrose in Ringer's solution should be given. In such cases the insertion of an intravenous cannula before the operation is begun is advisable, for through it the flow can be regulated more accurately than through a needle, and a large quantity injected quickly if shock appears. After the operation a transfusion of blood may be given through the same cannula. The precaution should be taken before operation of having a donor matched for transfusion. It is important in shock not to let the blood pressure go too low. Some individuals are more susceptible to the damaging effects of low blood pressure than others. Particularly in elderly people shock and low blood pressure, when extended over a long period of time, may result not only in cerebral impairment impossible to overcome even by transfusions, but may act deleteriously upon the functions of the liver and kidneys.

Cancer of the stomach does not usually demand emergency surgery, but a much larger number of cancers of the stomach perforate than it is generally supposed. Dr. Margaret Warwick[3] reported in a series of necropsies on 176 cancers of the stomach 27 deaths from perforation. It has been considered that perforation of the stomach is from a benign peptic ulcer, but it is important to bear in mind that cancer of the stomach frequently kills by perforation while the disease is still confined to the stomach. This brings up a new problem, for while a perforated benign peptic ulcer should usually be treated simply by suturing the perforation, decompression of the stomach by a Jutte or Levine tube, and intravenous dextrose in Ringer's solution, such treatment would not be applicable to a perforated cancer of the stomach. Cancerous tissue doubtless would not heal, and the manipulation of cancer would probably cause an extension of the disease. A partial gastrectomy should be done for perforation by cancer, even though it adds considerably to the immediate risk.

Operation for perforation of a peptic ulcer of the stomach or duodenum should be as prompt and as simple as possible. The fluid in the peritoneal cavity is quickly removed by suction and the ulcer exposed. It is commonly in the anterior wall of the first part of the duodenum, and often surrounded by flakes of lymph. It is closed in a transverse direction by a few mattress sutures of fine chromic catgut. Another row of the same kind of sutures is placed, and their ends are left long, passed through adjacent

peritoneal covered fat and tied down snugly. Usually nothing more should be done. The fluid under the diaphragm must be fully removed by suction. Only cases of more than eight or ten hours' duration should be drained. The patient is placed in bed in a sitting posture.

If there is perforation from cancer, drainage should be placed after a partial gastrectomy both locally and in the pelvis. This is done not only for the sepsis, but in order to prevent the implantation of cancer cells.

Gastric hemorrhage usually is from a peptic ulcer and in most cases may be controlled by medical measures. If, however, the bleeding is severe or is often repeated, an operation, including the resection of the bleeding lesion, is indicated. If the hemorrhage is from engorged veins caused by affections of the liver or spleen, the coronary vein with the tissues around it on the lesser curvature of the stomach may be doubly ligated and divided, as advocated by Waltman Walters.

An important feature of emergency surgery of the stomach and duodenum is postoperative hemorrhage. This is not often seen now. When in gastroenterostomy, especially by the clamp method, the anterior margins of the gastric and jejunal incision were merely folded in by a continuous right-angle suture, bleeding from the anterior margins of the stoma was by no means uncommon. Now that this fault of technic has been almost eliminated, either by suturing the stomach and jejunum in different layers or by doing the gastroenterostomy without clamps and controlling the vessels as they appear, postoperative hemorrhage rarely occurs. There is almost always from the raw surface in gastroenterostomy some oozing which is usually of no consequence. After every stomach operation a Jutte or Levine tube should be inserted through the nose into the stomach, and intermittent or continuous suction made. This removes gas and fluid, the stomach contracts, and there is less tendency to bleed because of the contraction of its wall. The same condition applies as in uterine bleeding when the womb is emptied in order to have it contract. If bleeding after an operation on the stomach cannot be controlled by free irrigations through a large stomach tube of hot tap water or hot salt solution at a temperature of about 120°, the abdominal wound should be opened. An incision is made in the anterior wall of the stomach, and with the fingers below the transverse mesocolon the stoma of the gastroenterostomy is pushed up to the anterior wall of the stomach. The bleeding spot can be readily recognized and whipped over with sutures or, if there is a general oozing around the stoma, its entire margin can be sutured. If the bleeding follows a partial gastrectomy a longitudinal incision is made in the anterior wall a short distance from the line of sutures. The sutures placed in the gastro-enterostomy or in the partial gastrectomy should not be disturbed.

A postoperative complication after gastro-enterostomy that is not so frequent now as formerly is failure of the stomach to empty. In most cases if the operation is properly performed there is but little trouble from this source, but occasionally if there is slight infection around the gastro-enterostomy and plastic peritonitis develops, the emptying may be so much delayed as to require a further operation. If the obstruction is from some kinking of the intestine by adhesions they may be separated, but often plastic peritonitis produces the kinking, and freeing the loop will not suffice. Manipulation around the site of the stoma in such cases will frequently increase the inflammation and exudate. It is best to leave this field, then, untouched except for such exploration as may be necessary to determine the cause of the trouble.

Two procedures are open to choice in this condition. One is to do a jejunostomy farther down, preferably by the simple method of Hendon, placing a mushroom catheter in the jejunum and bringing it out through a stab wound to the left of the incision. The material from the stomach can be aspirated and injected into the jejunostomy. In the course of several days the exudate around the gastro-enterostomy may be absorbed. Another method, and probably a surer one, though it requires more manipulation, is to bring up a loop of jejunum not involved in the exudate and do an anterior gastro-enterostomy; then an entero-enterostomy is made between the two limbs of the loop farther down.

The need for operation in this complication is infrequent, but if gastric lavage for a few days does not result in the stomach's emptying satisfactorily, something in operative correction of the condition must be seriously considered.

The after-treatment of emergency gastric or duodenal operations differs not materially from the after-treatment of other stomach operations, except of course that shock may be more common and intravenous administration of dextrose in Ringer's solution should be freer and transfusion of blood resorted to more readily. It is highly important that the stomach should be given as

much rest as possible, and at the same time that dehydration of the patient be avoided, and calories as well as the electrolytes should be supplied through the veins. In this way true physiologic rest is afforded the stomach and the patient is not too depleted to promote healing. If a Jutte or Levine tube is in the stomach the patient can have through the mouth practically as much water as he wishes. This only serves to wash out the stomach, the water is returned almost immediately through the tube, and not enough of it is retained to produce distention or tension on the sutures. The psychological effect on the patient is also advantageous. There is no point in beginning oral nourishment in these patients too soon, if intravenous dextrose in Ringer's solution is kept running continuously for two or three days. A rate of 150 c. c. an hour can usually be maintained. This furnishes about 700 calories and the electrolytes. The intake in the stomach should be carefully measured and compared with the output. When it is ascertained that the intake exceeds the output, a small amount of liquid diet can be given. If this goes well, the diet is increased, remembering that even after several weeks the food should still consist of smooth diet and no roughage.

When there is sepsis, as after an old perforation with localized peritonitis, or gross contamination, the suggestions that have been so forcibly advocated by H. A. Gamble[4] of leaving the abdominal wound open as far as possible should be followed. The peritoneum is sutured and possibly a few loose sutures are placed in the abdominal wall if there is danger of eventration, but most of the wound is kept open and loosely packed with iodoform or vaseline gauze.

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DISCUSSION (*Abstract*)

Dr. Harvey B. Stone, Baltimore, Md.—Dr. Horsley has very wisely opened his paper by reference to conditions that may be confused with emergency situations in the stomach and duodenum. As he points out, coronary occlusion is most difficult at times to distinguish from a stomach disorder and, in fact, may escape the recognition of the most experienced. Operation by mistake in cases of coronary occlusion is, naturally, to be regarded as a most unfortunate error. Nevertheless, it is the expressed opinion of experienced internists that in cases of grave doubt it is wiser to explore rather than to permit a possible surgical lesion of the stomach to go uncorrected. The same advice applies to those injuries of the abdomen by blunt force without penetration in which it cannot be decided with certainty that the stomach is or is not ruptured. Here, too, it is better to operate unnecessarily on a mistaken diagnosis than to withhold operation when such a rupture has actually taken place. Of course, the penetrating wounds of the abdomen which may involve the stomach do not present this problem at all. Almost without exception, they call for prompt exploration and the repair of whatever damage may have been done.

The frequency of perforations in malignant growths of the stomach, quoted by Dr. Horsley, is surprisingly high and his comments on the necessity of the more radical handling of such perforations than those due to peptic ulcer are entirely sound. Also, the advisability of drainage in these cases because of a more highly infectious type of soiling seems reasonable, but one wonders whether drainage would make any difference in the probability of metastatic implants.

Hemorrhage from the stomach as a reason for emergency surgery is a matter of dispute at the present time, but certainly, in this country, the general opinion is that expressed by Dr. Horsley, namely, that often repeated or otherwise uncontrollable bleeding may require operation. Operation is not to be considered, however, as a routine first resort in bleeding. Dr. Horsley's comments on the decreasing frequency of postoperative complications in gastric surgery, particularly bleeding and obstruction, coincides with our experiments. Improved operative technic and better care before and after operation no doubt explain much of this improvement. Such misfortunes still occur, however, and should be treated along the lines laid down in Dr. Horsley's paper.

Dr. L. Clarence Cohn, Baltimore, Md.—Dr. Horsley has spoken of a region of the body which is very vulnerable when subjected to trauma, infection or tumor formation, and has stressed the necessity not only for the differentiation of lesions above from those below the diaphragm, but has called attention to the fact that certain extra-gastric lesions may masquerade as intrinsic lesions of the stomach or duodenum and has intimated that it is not always possible to establish the diagnosis prior to operation.

After trauma our first responsibility is to prevent shock or to treat that complication first if it is already present at the time of the examination.

The treatment of any infection, whether in the peritoneal cavity caused by a perforated viscus or other lesion or elsewhere, aims at the localization of the infection and the prevention of diffuse involvement or septicemia. This is most readily accomplished by early diagnosis and application of the accepted treatment, which in the case of a perforated viscus is closure of the perforation and accessory measures.

For cancer we aim at the removal or the destruction of the disease before metastasis has occurred.

There are few of us present who have had or will have such experience in gastric surgery as Dr. Horsley has had. The number of stomach cases in the wards of my former chief, the late Dr. Bloodgood, at St. Agnes Hospital, was never very large; perhaps two or three cases at a time. However, these cases were studied both pre- and postoperatively very thoroughly, and there are x-rays before and after operation of almost every type of stomach lesion and of almost every type of stomach operation. Dr. Bloodgood followed Billroth's principle of suture, using three rows of interrupted silk. The fine black silk was adapted from Halsted. In later years a continuous suture of fine catgut replaced the interrupted silk suture in the mucous membrane. In making the anastomosis after gastric resection at the beginning he used the Billroth I anastomosis, later discarding it for Kocher's method of gastric-duodenostomy, returning again in 1924 to the Billroth I. When this could not be done he used Balfour's modification of Polya's operation with a long loop of jejunum.

For duodenal ulcer when operation was indicated the choice was Finney pyloroplasty rather than gastro-jejunostomy, and in larger chronic ulcers pyloric resection, and he felt that gastro-enterostomy was an operation of necessity rather than of choice.

There is a gastric lesion which requires emergency surgery to which I should like to call attention. There are more than one thousand cases of gastro-jejunal ulcer reported in the literature and more than one hundred cases of acute perforated gastro-jejunal ulcer for which the treatment in most instances has been simple closure of the perforation or closure of the perforation combined with closure of the gastro-enterostomy stoma.

Dr. Horsley (*closing*).—Like Dr. Stone, I, too, was surprised at the number of deaths that cancer of the stomach causes by perforation. I recall vividly a patient who had a large ulcer in the pyloric end of the stomach and who was to have a partial gastrectomy. About an hour before the time set for the operation there was perforation. The patient was operated upon, and a partial gastrectomy was done. Histologic examination showed that the growth was cancerous. He made a satisfactory immediate recovery, but died three years later of recurrence.

I am also somewhat surprised that Dr. Stone, who has done brilliant work in transplantation of the culture of parathyroid cells, cannot visualize the removal of cancer cells by drainage after perforation of a gastric cancer. Of course, after the cancer cells have become fixed in the tissues, drainage would have little or no effect upon them; but when a gastric cancer perforates it seems highly probable that, along with the leukocytes and the bacteria, cancer cells from the perforation are also floating in the abdominal fluid. If this fluid can be removed within the first few hours, it is likely that some cancer cells that have escaped from the tissue of the perforation will also be removed. We know that cancer cells from the stomach and upper abdominal cavity are implanted in the peritoneal cavity lower down by gravity, but there must be a period of time between the throwing off of a cancer cell from the original lesion and the time at which it is firmly engrafted in the peritoneum, when it might be removed by drainage.

ELLIOT TREATMENT IN PELVIC INFECTIONS*

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My purpose in presenting this subject before the Section is to promote a discussion of the value of prolonged heat by the use of the Elliot technic in the conservative treatment of pelvic inflammatory diseases. Any new procedure in the treatment of inflammations of the female pelvis that will reduce the period of disability, increase the percentage of cures and diminish the number of mutilating operations on women in their period of reproductive life is worthy of discussion.

The use of heat to alleviate pain and promote healing of acute and chronic inflammation dates back to antiquity. The ancients appreciated the value of applying heated solid bodies to relieve abdominal cramps and they used hot poultices extensively to cure inflammation. Hippocrates as far back as 450 B.C. used the hot douche for relief of pelvic pain. Forgotten for one thousand years, the hot douche was revived by Galen and Celsus. Then chiefly because the Moslem religion prohibited male physicians from examining the female genitalia, gynecology became a lost art. German physicians in the Eighteenth Century, in order to increase the duration of therapeutic heat in the pelvis, heated lead shot and poured them into the vagina. In the Nineteenth Century, Emmett condemned the use of intra-uterine douches and advocated the treatment of pelvic inflammation by the use of hot vaginal douches and was convinced that he cured many patients. No further progress was made in this form of therapy until Gellhorn, in 1924, showed that the vagina can stand a much higher temperature than the vulva and perineum. By protecting these parts with vaseline he was able to give a vaginal douche using two gallons of water at a temperature of 120° F. He thus treated pelvic inflammation, subinvolution and pelvic pain with very gratifying results.

For a number of years gynecologists have applied heat by means of medical diathermy. This method, aside from the fact that opinions differ concerning the results obtained, requires a costly

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apparatus and special knowledge and experience with the diathermic current. Burns of the vaginal mucous membranes have been reported following its use. The rugae of the vagina are not obliterated by distention so that the increase of local temperature is not uniform, thus increasing the danger of burns of the mucosa.

At about the same time that Gellhorn made his observations, Dr. Charles Robert Elliot likewise noticed the lesser sensitivity of the vagina to heat. He constructed an apparatus for the prolonged application of dry heat to the vagina which consists of a thin, distensible rubber vaginal applicator through which, by means of an inflow and outflow tube, water heated to any desired temperature is made to circulate at a controlled pressure. The vaginal bag fits snugly around the cervix and when dilated distends the vagina and distributes the heat equally in all directions. The treatment is started at 115° F. and the heat increased ¾ of a degree per minute until a temperature of 128 to 130° is reached and maintained for one hour. Holden and Gurnee have shown that in patients having a normal mouth temperature the treatment will produce a temperature in the vagina of 125° F, the cervix 112° F., the anterior rectal wall 104.2°, 104° F. in the urethra and 106° in the intra-abdominal cul-de-sac. It is reasonably assumed that the temperature of the uterus, adnexa and broad ligaments are similarly affected.

The technic used is as follows: the patient is given a cleansing enema and allowed to empty her bladder. A speculum is inserted and the vagina cleansed of discharge. The bag is introduced into the vagina empty of water, folded and thoroughly lubricated. The tube leading to the bag is wrapped with moist gauze or cotton to protect the sensitive skin of the vulva from heat; the bag is then filled with water at a temperature of 115° F. and distended to 1 to 2 pounds pressure. After the pressure is established it is well to insert the finger into the vagina to be certain that both arms of the bag are distended and have found their way into the lateral fornices of the vagina, for it is important that the vagina be distended and the heat carried high into the pelvis. The temperature is gradually increased during the first 10 or 15 minutes to the maximal temperature the patient will tolerate comfortably. After the second treatment 128 to 130° F. can usually be attained without difficulty. The temperature and pressure of 1½ to 2½ pounds is maintained for one hour. We feel that adequate pressure sufficient to distend the upper vagina and apply the applicator to the cervix and vaginal fornices is necessary for adequate dissemination of heat. The pressure indicator on the machine is used to avoid excessive pressure, but the finger in the vagina or rectum is used to be sure adequate pressure is maintained. It is better to maintain full vaginal distention at a lower temperature than to have inadequate pressure at 130° F. Women vary greatly in their tolerance to both heat and pressure, which must be determined for each case.

The uniform radiation of heat causes a marked and prolonged hyperemia of the pelvic organs, accompanied by a profuse discharge of cervical and vaginal secretions. After two or three treatments there occurs a distinct softening of the cervix which actually becomes shorter and broader, causing a widening of the cervical glands. There is a marked relief of pain and tenderness, and with continued treatment the uterus and adnexa are more easily outlined, mobility of the uterus is increased and the inflammatory exudate is gradually absorbed. The elevation of temperature causes a destruction or attenuation of the organisms and in 87 per cent of cases Holden and Gurnee have shown a 17 per cent increase in leukocytosis following the treatments.

This method was first used by Holden and Gurnee,[1] of Bellevue Hospital, in all types of acute and chronic inflammation. In 1931 they reported their results in 150 consecutive cases and at that time had given over 5,000 treatments to about 500 cases. They reported 81 per cent of their cases either clinically cured or considerably improved. In 35 cases of gonorrhea 31 were free of demonstrable organisms after approximately twenty treatments; the remaining four cases required cauterization of Skeene's ducts before a cure could be affected. Grouping all classes of pelvic inflammatory disease treated they found by comparing their cases with a former series of similar cases under other treatment that the time of hospitalization was considerably shortened.

Randall and Counsellor,[2] of the Mayo Clinic, reported a group of 125 cases with satisfactory results in 77.2 per cent and recommended its use both preoperatively and postoperatively.

Holden and Sovak[3] used the Elliot treatments before and after plastic operations on the oviducts, and Sovak[4] in a recent paper said that all of his cases routinely receive Elliot treatments whether the tubes are patent or occluded, "for it is our impression that the heat applied by this method aids materially in reabsorption of any postoperative inflammatory tissue reaction."

Other authors who have had favorable experiences with this method of treatment of pelvic infections include Graham,[4] Counseller,[5] Sanders and Sellers,[6] Doan and Simpson[7] and Fallas.[8]

The series of 100 cases providing the material for this report were treated during an 18-month period from April, 1935, to November, 1936. For convenience in determining the results obtained I have divided them into 8 groups representing different pathological conditions.

There were five cases of acute gonorrhea with the infection confined to the cervix and urethra. No local treatment except routine cleanliness of the external genitalia was used. Local applications and instrumentation were carefully avoided. The number of treatments per case varied from 16 to 32 with an average of 26 treatments. Treatment was continued until three successive negative smears from both cervix and urethra were obtained. Observation was continued through three successive menstrual periods, when additional smears were examined and all five cases discharged as cured.

In twelve cases the infection was chronic in character and confined to the cervix or to the cervix and urethra. The number of treatments ranged from 12 to 24 with an average of 18 treatments per case. Excellent results were obtained in four cases, or 33 1/3 per cent, without further treatment, while 7 cases, or 58.3 per cent, were markedly improved in that the discharge, pelvic pain and backache were relieved and smears became negative, but cauterizations were necessary in order to clean up erosions and cystic cervicitis. A patient 60 years of age who had supravaginal hysterectomy and bilateral salpingo-oophorectomy twenty years before and who had suffered for years with a profuse discharge from a gonorrheal infection in the cervical stump, failed to improve after 28 treatments. The cervix was cauterized, but she did not return for further observation and was classified as unimproved. In 91.6 per cent of cases of chronic infection treated the latent foci of gonococci were cleared up by use of Elliot treatment. Erosions and cystic cervicitis required cauterization.

Thirty-two cases of acute salpingitis were treated with from 14 to 35 Elliot treatments, the average being 21. Additional therapy included rest in bed, hot water bottle to abdomen, bland diet, bowel hygiene and sedatives as required. In 24, or 75 per cent, of cases the results were excellent: they were discharged as clinically cured and free from gonococci. In 5 cases, or 15.6 per cent, although there were residual masses in the pelvis following the course of treatments, they were gonococcus and symptom-free and were discharged as improved. Three cases, or 10 per cent, although improved, eventually required surgery for relief of symptoms. We feel that greater conservation of tissue was possible on account of the previous Elliot treatments.

In this series there were twenty-seven cases of subacute or chronic pelvic inflammatory disease of long standing with one or more recurrent acute exacerbations usually with large inflammatory masses in the pelvis. Formerly, practically all of this type were operated upon. Of this group ten cases, or 37 per cent, were discharged as well, as bimanual examinations failed to reveal tenderness, palpable masses or pelvic induration. Nine cases, or 33.3 per cent, were discharged free of subjective symptoms, but still revealed palpable masses or thickening of adnexa or discharge. Eight cases, or 29.6 per cent, although definitely benefited by Elliot treatments, required operation. We feel that in this group less radical surgery was possible, more tissue was conserved and postoperative morbidity was lessened when heat was used as a preoperative measure. Furthermore, the treatments served as an invaluable aid in separating the definitely surgical cases from those in which relief could be obtained by conservative treatment.

Four cases of cul-de-sac abscess were treated before and after colpotomy had been performed, with good results. Although Holden and Gurnee reported absorption and resolution in 20 out of 23 cases of pelvic abscess after fluctuation appeared, we felt that by colpotomy as soon as fluctuation appeared the number of hospital days would be reduced. The average number of treatments per case was 16.

A case of specific vaginitis in a patient 62 years of age, in whom a complete hysterectomy

had been performed, failed to respond to 28 treatments. She could not tolerate the heat over 124° F.

Six postpartum infections and eight infected abortions were treated with complete relief in twelve cases, or 85.7 per cent, and marked improvement in two cases, or 14.3 per cent. All of these cases were acutely ill with fever and marked pelvic and lower abdominal tenderness. Treatments were usually given twice daily until the acute symptoms subsided. All of this group showed marked improvement within two or three days with rapid disappearance of pain and distention. An average of sixteen treatments was given in each case.

Five cases of subinvolution were completely relieved with an average of eight treatments. In every case there was a rapid disappearance of symptoms of backache, heaviness in the pelvis as well as reduction in size of the uterus.

Burns following use of the Elliot treatments occurred in five instances in this series and were not severe enough to discontinue the treatment. They occurred in our early use of the machine and were due to imperfect technic. The burns were in the vaginal fornices or on the cervix and appeared as small gray areas of slough 2 to 3 cm. in diameter when examined by speculum before the following treatment. All healed within two weeks without scar formation.

Elderly patients with a senile vagina and those with extensive vaginal plastics do not tolerate heat well and burns are more likely to occur on account of the sluggish circulation of the tissues.

SUMMARY

A consecutive series of 100 cases of pelvic inflammatory and allied diseases are reported in which the principal treatment besides time and rest consisted in the use of prolonged heat by the Elliot technic. A total of 2,008 treatments were given with an average of 20 treatments for each case. In 64 per cent of cases the results were considered excellent and these cases were discharged as clinically cured. Twenty-three per cent were discharged completely relieved of subjective symptoms and thus avoided major surgical treatment. Thus in 87 per cent of cases the results from Elliot treatments alone were satisfactory. Eleven per cent of cases were improved by heat treatments which permitted less radical surgery than would have been possible otherwise. Two per cent of cases showed no improvement.

It is hoped that these results and the results reported by other authors will increase conservatism in the treatment of pelvic infections and thus reduce the mortality, lessen morbidity, and conserve function of the pelvic organs of women in their active reproductive life.

CONCLUSIONS

(1) The Elliot technic is an effective and safe method of applying prolonged heat to the pelvic organs.

(2) Satisfactory results may be obtained in the great majority of cases of pelvic inflammatory disease, whether of postpartal, postabortal or specific origin.

(3) The latent focus of infection in the cervix is readily cleared up through the effect of heat and increased drainage.

(4) In acute gonorrhea, the Elliot treatment is an improvement over former methods in both safety and rapidity of cure.

(5) The treatments serve as an invaluable aid in separating the definitely surgical cases from cases in which clinical cure could be obtained by conservative means.

(6) When surgery is necessary, the preoperative use of Elliot treatments reduces the extent of operative interference and thereby conserves tissue.

(7) The earlier the treatments are started and the more recent the infection, the better the prospects for complete cure.

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DISCUSSION (*Abstract*)

Dr. Chas. J. Andrews, Norfolk, Va.—The use of heat in the treatment of pelvic inflammatory disease is a

time-honored procedure. Since the introduction of the Elliot technic it has become possible to apply it in a more accurate and uniform manner. The conservative treatment of pelvic inflammation seems to be well agreed upon by all, but the Elliot technic is a comparatively new method, and is still on trial. To one who treats a few cases only it is possible to become enthusiastic if the results appear good.

Considering the tendency of inflammatory disease to recovery, it is possible that we sometimes give undue credit to the treatment.

Several very notable reports of series of cases treated by the Elliot method have already been published. Most of these have been encouraging and report satisfactory results in from 80 to 100 per cent in cases treated. The excellent record which Dr. Lucas has presented here today goes far, particularly when added to those preceding it, to place this method on a firm foundation.

My own experience with this method has been like that of Dr. Lucas extended over a short time, not much more than eighteen months, and has been composed of private patients, and mostly ambulatory cases; a total of about 75 in all, with about an average of ten treatments each. This has included all the classes mentioned except puerperal or post-abortal cases, which I shall include when suitable cases are encountered. My impression is that the most striking results were with acute gonorrhea. Here it is difficult to evaluate the results. We have all seen gonorrhea in the female ended very soon by very simple treatment, and other cases more virulent treated in the same way without effect and progressing until the pelvic organs were practically destroyed. I have had at least one case which appeared when first seen to be quite virulent, with beginning salpingitis, which made a rapid recovery. Three of my gonorrheal patients developed a rather severe temporary menorrhagia following a course of treatment. So far no burns have occurred, though I use somewhat higher pressure than that used by Dr. Lucas, usually about three pounds. I do, however, follow very closely the rules recommended. I feel quite sure that in some of my acute cases convalescence of pelvic inflammation has been greatly hastened and operation avoided. A few of my rather acute hospital cases and one or two chronic ones complained severely of the treatment and it was necessary to discontinue it, but with these few exceptions the patients were enthusiastic.

Trichomonas infection of the vaginal tract has recently been added to the indications for the Elliot treatment. Methods previously used have controlled this condition fairly well, and since using the silver picrate method I have felt that the recurrences had been prevented in nearly all instances. A recent case which was apparently not benefited by any treatment has been treated by the Elliot method with obvious improvement. At present this is only a suggestion, as so far this has not been used long enough to form any opinion of it.

On the whole, the conclusion that the Elliot apparatus is a useful instrument seems to be justified. Dr Lucas' paper is, I believe, a valuable contribution to our knowledge of what may be expected of it.

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New Orleans, Louisiana, November 30-December 1-2-3, 1937

NEW ORLEANS MEETING

Despite strikes and uncertainty of the coming course of taxes, the depression would now seem to be a dim and receding cloud. The general public is again conscious of its need of medical attention and hospitals are as crowded as in 1927. The Southern Medical Association met in New Orleans in 1924, thirteen years ago, and again in New Orleans in 1930. This largest and oldest Southern city is preparing to charm the medical sightseer and investigator in 1937. The local meeting place for the November convention has been chosen, the Municipal Auditorium, which is in easy walking distance of most of the hotels and will provide ample space for every section.

SECTION PROGRAMS

Programs of the seventeen sections and conjoint meetings are under construction. Some are nearly complete. It is desired to have as varied a subject matter as possible to cover all new medical movements of significance. New contributors from the South will be welcomed. The section officers will very gladly receive suggestions as to men and subjects for the coming meeting. Physicians who desire a place on the November program should communicate with the secretary of the section to which the work seems allied and submit the title of the paper which they desire to present. The subject matter should be outlined if possible. Any Southern physician who has new work to report is urged to write for a place on the program. A list of the groups which will convene and officers of each is to be found on page 562.

"It is later than you think," half the year is gone, and many places have been filled. Applications for the program should be sent to section secretaries at the earliest possible date.

SCIENTIFIC EXHIBITS

Scientific exhibits will again be extensive. Men with new work to present in the form of an exhibit should communicate directly with the Association office in Birmingham. Exhibits are acceptable which have a teaching value or depict an original idea. A limited space is available for the various subjects, and requests for space should be mailed to Birmingham as soon as possible with a description of the material to be displayed.

INFLUENZA VIRUS

Nothing is more interesting than the cause of influenza and colds to the average individual who is made miserable by the condition once or twice per year. Study of respiratory infections was greatly advanced by the report of Laidlaw[1] and his associates in 1933 that characteristic symptoms resembling human influenza could be induced in ferrets by inoculating them with filtered nasal washings from human cases of influenza. This supplied a fairly convenient small laboratory animal. After the virus had been adapted to ferrets, it could be transmitted to mice which had been anesthetized. In these animals it led to a serious disease which was often fatal; it usually took the form of pneumonia. Since the mice did not sneeze or cough, germs were less freely spread from them, they could be more readily controlled, and were more satisfactory experimental animals than the ferrets. The same virus has been reported isolated from

1. Smith, Wilson; Andrews, C. H.; and Laidlaw, P. P.: A Virus Obtained from Influenza Patients. Lancet, **225**:66, 1933. Laidlaw, P. P.: Epidemic Influenza: A Virus Disease. Lancet, **228**:118 (May) 1935.

influenza epidemics in different parts of the world. Failure to isolate it from various epidemics has also been noted. Francis and Magill[2] have described isolation of influenza virus from patients in New York City, and direct inoculation into mice without the preliminary ferret passage. They have also succeeded in growing it in tissue culture and on egg membrane. Hoyle and Fairbrother,[3] of the University of Manchester, recovered Laidlaw's virus from an influenza epidemic and studied the immune reactions of the blood of convalescents and of exposed persons who escaped infection. Complement-fixation increased after an attack and was for the most part high in exposed persons who did not develop symptoms.

The studies on animal transmission are enlightening as showing how a micro-organism originally not virulent for an animal may adapt itself to a new species. The mouse was rendered susceptible to influenza virus by anesthesia. X-radiation of small animals may make them susceptible to typhus. After the influenza virus had developed in an injured animal, it became virulent for normal members of the species, and in the case of the mouse the formerly harmless virus caused a fatal disease. Similarly one may imagine the adaptation of an animal pathogen to man if it first is able to establish itself in a human being of lowered resistance.

A very large number of human infectious diseases begin with a cold: the majority of the diseases of childhood as measles, mumps, scarlet fever, diphtheria, infantile paralysis, even congenital syphilis may be characterized by snuffles. The early symptoms are indistinguishable from influenza, but the cause of these is known.

It would appear that the upper respiratory tract is an antechamber which detains and is capable of destroying many types of pathogenic bacteria. Some overwhelm its defense to produce severe systemic symptoms. Its characteristic response to attack is a cold. Specific prevention of human colds, which may result from a hundred bacterial causes, would still seem a very remote hope.

2. Francis, Jr., Thomas; and Magill, Thomas P.: Direct Transmission of Human Influenza Virus to Mice. Proc. Soc. Exp. Biol. & Med., **36**:132 (March) 1937. Ibid: Direct Isolation of Human Influenza Virus in Tissue Culture Medium and on Egg Membrane. Proc. Soc. Exp. Biol. & Med., **36**:134 (March) 1937.

3. Hoyle, Leslie; and Fairbrother, R. W.: Isolation of the Influenza Virus and the Relation of Antibodies to Infection and Immunity. Brit. Med. Jour., No. 3977:655 (March 27) 1937.

BIRTH CONTROL LEGISLATION

For many years Margaret Sanger has been known as a distinguished and sincere worker for a humanitarian cause. It has been held an infringement of the Federal constitution for any person, medical or lay, to dispense information regarding contraception. As president of the National Committee on Federal Legislation for Birth Control, and in other capacities, Margaret Sanger has worked tirelessly for revokal of the law, has organized birth control clinics in many cities in America and abroad, and like the early suffragists has considered it an honor to be imprisoned for her convictions. In 1916 she served a thirty-day jail sentence.

Victory is now claimed by the committee on birth control legislation. No new law has been passed or old law revoked, but in a recent test case before the United States Circuit Court of Appeals the decision is considered conclusive. It is called by the committee "a bill of rights for the medical profession, liberating it from the restrictions imposed by the Comstock law enacted over sixty years ago." The case concerns the right of a physician to import Japanese pessaries for research purposes, and the decision of the court reads:

"We are satisfied that this statute * * * was not to prevent the importation, sale or carriage by mail of things which might intelligently be employed by conscientious and competent physicians for the purpose of saving life or promoting the well being of their patients."

Since the Government rests its case and will not carry it before the Supreme Court, the decision has the effect of legislation. The court, reinterpreting an old statute in the light of modern times, reverses a meaning which the law has held throughout this century. One wonders what the author of the bill might say if he heard the present day court's explanation of his intention in framing it. But Comstock himself would be a different man if he lived in modern times.

The court in this instance is as potent and active a law-maker as Congress. One sees illustrated here the difficulty of keeping the legislative, executive and judicial functions of the Government separate and distinct.

GLEANINGS FROM RECENT JOURNALS

Stomach Motility and Functional Tests.—In the customary diagnostic methods of introducing a test material into one part of the body, as into the alimentary tract or blood stream, then looking for it in another after a specified time, as in the gallbladder, blood or urine, many variables must be taken into account. For examination of the gallbladder the radiopaque test material, phenoltetraiodophthalein, may be injected into the blood stream to avoid the intervening stomach. The phenolsulfonphthalein test of kidney function is also done by injecting the test dye into a vein, which eliminates the factor of absorption from the alimentary tract. If the test substance is taken by mouth, the influence of the stomach should be considered. In the glucose tolerance test for carbohydrate assimilation and in the urea concentration test of kidney function, glucose or urea is taken by mouth and the quantity in blood or urine is subsequently measured. In these two methods the effect of the intervening stomach is usually disregarded.[1]

Apperly and Cary,[1] of the Medical College of Virginia, have compared glucose tolerance and urea concentration tests in patients whose gastric function has also been studied under the x-ray. The fast-emptying stomachs were those which emptied the fractional test meal in one hour or less. The slow-emptying were those which showed gross retention of the barium meal after six hours. They report that patients with high gastric motility have an early peak of the glucose curve; while in patients with slowly emptying stomachs there is a delayed rise of the blood glucose, the entire curve is low and flat, and there is a marked delay in the return to the fasting level.

A low fasting blood glucose was observed, averaging around 75 milligrams, in patients with rapidly emptying stomachs. Patients with slowly emptying stomachs usually had a higher fasting sugar level. They were also usually older than those with fast-emptying stomachs. The average age for the slow-emptying was forty-two years, and for the fast-emptying twenty-eight. The older patients, then, had a lower stomach motility, and they also had less volatile blood sugar levels. The results of the urea concentration test were of the same order as the glucose tolerance.

One may conclude as a corollary that young patients probably have a lower morning blood sugar than those of middle age and consequently a greater need for breakfast before the day's work begins, though older persons may feel an irregularity of meal hours more keenly than the young.

Gastric Juice of Pernicious Anemia.—The volume of stomach secretion is greatly diminished in pernicious anemia, according to Goldhamer,[1] of Ann Arbor. In this disease the average secretion is 20 c. c. per hour as opposed to a normal of 150 c. c. During remissions the volume usually increases, but there is no return of free hydrochloric acid. The volume diminishes also merely with age. If gastric juice is collected from patients in induced remissions of the disease and stored in the ice box with hydrochloric acid, it may be used to induce remissions in other cases of pernicious anemia, just as normal stomach juice does. The gastric deficiency in pernicious anemia Goldhamer considers to be quantitative, as he has suggested before, rather than absolute.

One would expect a delayed gastric motility in pernicious anemia as a result of slow digestive action of the greatly reduced amount of digestive juice.

1. Apperly, Frank L.; and Cary, M. Katharine: Effect of Gastric Motility on Urinary Urea Concentration Test and Glucose Tolerance Test. Jour. Lab. & Clin. Med., **22**:395 (Jan.) 1937.

TWENTY-FIVE YEARS AGO

From Journals of 1912

Has Cod-Liver Oil Any Value?[2]—* * * "'Cod-liver oil' has long been a name to conjure with in medicine, and no one has done more to invest it with hypothetical virtues than the practitioner himself. Until it shall be demonstrated that cod-liver products have some efficiency other than that presented by any easily digestible fat we must hesitate to look on them as anything more than available foods."

Winslow's Soothing Syrup Barred in Australia.[3]—"The Board of Health of New South Wales has prohibited the advertising and sale in that commonwealth of Mrs. Winslow's Soothing Syrup as being injurious to life. * * * We are optimistic enough to believe that the time will come, in a not far distant future, when a similar prohibition for this and similar dangerous nostrums will be operative in this country. The indiscriminate sale of such dangerous opium-laden products is a disgrace to any civilized community that permits it."

Dangers of Salvarsan.[4]—"Noguchi * * * makes one surprising statement to the effect that relapses after one dose of salvarsan are comparatively few. * * *

1. Goldhamer, S. M.: Gastric Juice in Patients with Pernicous Anemia in Induced Remissions. Amer. Jour. Med. Sci., **193**:23 (Jan.) 1937.

2. Editorial. A Recent Food and Drug Report. J.A.M.A., **58**:940, 1912.

3. The Propaganda for Reform. J.A.M.A., **58**:954, 1912.

4. Book Reviews. J.A.M.A., **58**:961, 1912.

"This work of Benario's is a piece of special pleading in behalf of salvarsan, its object being to show that the disquieting, not to say alarming, accidents to the nervous system arising in connection with the use of salvarsan are due to syphilis and not to salvarsan. * * *

"Benario, with painstaking thoroughness, defends salvarsan from the charge that it causes toxic injury to the central nervous system either directly or by causing a lessened resistance in these nervous structures to the attack of the *Spirochaeta pallida*. By comparing case histories of 122 patients treated with mercury with 177 treated with salvarsan, all having luetic lesions of the central nervous system during the early secondary stage, he seeks to prove that salvarsan is not followed by these lesions any oftener than is other treatment, but simply that the cases have not been reported—a line of argument that is not very conclusive. * * *

"He recommends, without a thought of danger, three doses of 0.4 to 0.6 gm. salvarsan, intravenously, at intervals of from five to eight days. That these are not wholly without danger no one who has followed the literature of salvarsan can doubt."

Book Reviews

The Fundamentals of Electrocardiographic Interpretation. By J. Bailey Carter, M.D., Clinical Instructor, Department of Medicine, Rush Medical College, the University of Chicago; Associate Staff, Cook County Hospital, Augustana Hospital, Chicago. With a Foreword by Horatio Burt Williams, M.D., Dalton Professor of Physiology, College of Physicians and Surgeons, Columbia University, New York. 326 pages, illustrated. Springfield, Illinois: Charles C. Thomas, 1937. Cloth $4.50.

The author has given a very complete and condensed discussion of electrocardiographic interpretation. The arrangement of the material is excellent. Before discussing the technicalities of electrocardiography a very good discussion of the physiology and the process of electrocardiography is given. The normal complexes are discussed and illustrated; following this the individual pathological wave changes are illustrated and explained. Various clinical entities causing electrocardiographic changes are briefly given and illustrative tracings are presented. A group of typical case histories and their electrocardiographic changes are discussed.

There are two features of this book that deserve particular commendation: a brief glossary explaining the terms used in electrocardiography which should be of help to one who is not familiar with the jargon of electrocardiography, and a very complete bibliography of recent contributions to the literature on the subject.

The Medical Record Visiting List or Physicians' Diary for 1937. Revised. Baltimore: William Wood Division, The Williams & Wilkins Company. Cloth, 30 patients per week $1.75; 60 patients per week $2.00; 90 patients per week $2.50.

An efficient and time saving method of keeping a record of the daily work done by the busy physician. It will be entirely satisfactory to the doctor who does not require detailed records.

Diseases of the Coronary Arteries and Cardiac Pain. Edited by Robert L. Levy, M.D., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Associate Visiting Physician and Cardiologist, Presbyterian Hospital, New York City. Advisory Editorial Committee: Alfred E. Cohn, James B. Herrick, Carl J. Wiggers. Contributors: Claude S. Beck; Herman L. Blumgart; Alfred E. Cohn; Louis I. Dublin; James B. Herrick; William J. Kerr; Robert L. Levy; Fred M. Smith; William C. Von Glahn; Joseph T. Wearn; James C. White; Paul D. White; Carl J. Wiggers; Frank N. Wilson. 445 pages, illustrated. New York: The Macmillan Company, 1936. Price $6.00.

This book has the advantages and the disadvantages which are inherent in any volume compiled by a number of different authors. Certain parts of it are excellent, notably the historical discussion of the subject by Herrick and the chapters an clinical significance of cardiac pain by White, and on electrocardiographic changes in coronary disease by Wilson. The latter chapter requires but will repay careful study. The sections dealing with the anatomy, physiology, pharmacology and pathology of the coronary arteries are well written, up-to-date and leave little to be desired. The same may be said of the chapters concerning the nerve supply of the heart and the therapeutic interruption of these tracts for the relief of pain.

The book suffers from the lack of uniformity in nomenclature. Some of the authors use the term "angina pectoris" in the sense of a clearly defined entity with a uniform physiologic basis—lack of oxygen in the myocardium—but brought about by various pathological processes. In other chapters written by different authors the term "angina pectoris" has been discarded and a vague concept of cardiac pain substituted. Such a difference of opinion would have been justifiable ten years ago but seems inexcusable now that the pathogenesis of angina pectoris has been clearly worked out, and that this syndrome has been sharply separated from other instances of cardiac pain.

In spite of the disadvantages mentioned the book is well worth having for it presents much modern information about a subject of great importance.

Laboratory Outline in Filterable Viruses. By Roscoe R. Hyde, Professor of Immunology and Director of the Laboratories of Immunology and Filterable Viruses, School of Hygiene and Public Health, The Johns Hopkins University with the assistance of Raymond E. Gardner, Associate in Immunology. 85 pages, illustrated. New York: The Macmillan Company, 1937. Cloth $1.50.

This manual, in Part 1, outlines five exercises on methods of filtration, four on bacteriophage, and nineteen on virus diseases. Part 2 outlines seven exercises on the histo-pathology of virus diseases. The course covers 24 half-day periods.

The outline of laboratory work supplemented with theoretical knowledge given in lectures is planned to give the student a first hand knowledge of the nature and behavior of a number of representative viruses, a comprehensive experience with the pathology of a selected group of virus diseases, and serves as an introduction to research in the virus field.

BOOK REVIEWS continued on page 563

OFFICERS 1936-1937

The following is a complete roster of the officers of the Southern Medical Association for 1936-1937, and of associations meeting conjointly with the Southern Medical Association:

President—Dr. Frank K. Boland, Atlanta, Georgia.

First Vice-President—Dr. Sydney R. Miller, Baltimore, Maryland.

Second Vice-President—Dr. Lea A. Riely, Oklahoma City, Oklahoma.

Secretary-Manager (Secretary, Treasurer and General Manager)—Mr. C. P. Loranz, Birmingham, Alabama.

Editor of Journal—Dr. M. Y. Dabney, Birmingham, Alabama.

Associate Editor of Journal—Mrs. Eugenia B. Dabney, Birmingham, Alabama.

Councilors—Dr. C. W. Dowden, Chairman, Louisville, Kentucky; Dr. M. Toulmin Gaines, Mobile, Alabama; Dr. Harvey S. Thatcher, Little Rock, Arkansas; Dr. Wm. Thornwall Davis, Washington, D. C.; Dr. Luther W. Holloway, Jacksonville, Florida; Dr. Edgar G. Ballenger, Atlanta, Georgia; Dr. Arthur A. Herold, Shreveport, Louisiana; Dr. J. Mason Hundley, Jr., Baltimore, Maryland; Dr. Harvey F. Garrison, Jackson, Mississippi; Dr. Alphonse McMahon, St. Louis, Missouri; Dr. Hamilton W. McKay, Charlotte, North Carolina; Dr. W. K. West, Oklahoma City, Oklahoma; Dr. Kenneth M. Lynch, Charleston, South Carolina; Dr. Eugene Rosamond, Memphis, Tennessee; Dr. Guy F. Witt, Dallas, Texas; Dr. Vincent W. Archer, University, Virginia; Dr. James R. Bloss, Huntington, West Virginia.

Board of Trustees (All are Past-Presidents)—Dr. Felix J. Underwood, Chairman, Jackson, Mississippi; Dr. Lewis J. Moorman, Oklahoma City, Oklahoma; Dr. Irvin Abell, Louisville, Kentucky; Dr. Hugh Leslie Moore, Dallas, Texas; Dr. H. Marshall Taylor, Jacksonville, Florida; Dr. Fred M. Hodges, Richmond, Virginia.

Section on Medicine—Dr. Chas. Hartwell Cocke, Chairman, Asheville, North Carolina; Dr. Henry G. Rudner, Vice-Chairman, Memphis, Tennessee; Dr. John B. Youmans, Secretary, Nashville, Tennessee.

Section on Pediatrics—Dr. Gilbert J. Levy, Chairman, Memphis, Tennessee; Dr. D. C. Wharton Smith, Vice-Chairman, Baltimore, Maryland; Dr. Hughes Kennedy, Jr., Secretary, Birmingham, Alabama.

Section on Gastroenterology—Dr. Harry Eldridge Murry, Chairman, Texarkana, Arkansas-Texas; Dr. Fred W. Wilkerson, Vice-Chairman, Montgomery, Alabama; Dr. Lay Martin, Secretary, Baltimore, Maryland.

Section on Pathology—Dr. Wiley D. Forbus, Chairman, Durham, North Carolina; Dr. Everett L. Bishop, Vice-Chairman, Atlanta, Georgia; Dr. Roy R. Kracke, Secretary, Emory University, Georgia.

Section on Neurology and Psychiatry—Dr. Lawrence F. Woolley, Chairman, Towson, Maryland; Dr. Frank H. Luton, Vice-Chairman, Nashville, Tennessee; Dr. S. Spafford Ackerly, Secretary, Louisville, Kentucky.

Section on Radiology—Dr. D. A. Rhinehart, Chairman, Little Rock, Arkansas; Dr. Hunter B. Spencer, Vice-Chairman Lynchburg, Virginia; Dr. Roy G. Giles, Secretary, Temple, Texas.

Section on Dermatology and Syphilology—Dr. Harry M. Robinson, Chairman, Baltimore, Maryland; Dr. J. Richard Allison, Vice-Chairman, Columbia, South Carolina; Dr. Winston U. Rutledge, Secretary, Louisville, Kentucky.

Section on Surgery—Dr. Alton Ochsner, Chairman, New Orleans, Louisiana; Dr. William F. Rienhoff, Jr., Vice-Chairman, Baltimore, Maryland; Dr. J. M. T. Finney, Jr., Secretary, Baltimore, Maryland.

Section on Bone and Joint Surgery—Dr. Guy A. Caldwell, Chairman, Shreveport, Louisiana; Dr. Alfred R. Shands, Jr., Vice-Chairman, Durham, North Carolina; Dr. J. Hiram Kite, Secretary, Atlanta, Georgia.

Section on Gynecology—Dr. John C. Burch, Chairman, Nashville, Tennessee; Dr. R. A. Ross, Vice-Chairman, Durham, North Carolina; Dr. John F. Lucas, Secretary, Greenville, Mississippi.

Section on Obstetrics—Dr. Warren E. Massey, Chairman, Dallas, Texas; Dr. John McF. Bergland, Vice-Chairman, Baltimore, Maryland; Dr. Milton Smith Lewis, Secretary, Nashville, Tennessee.

Section on Urology—Dr. Hamilton W. McKay, Chairman, Charlotte, North Carolina; Dr. Albert E. Goldstein, Vice-Chairman, Baltimore, Maryland; Dr. Jefferson C. Pennington, Secretary, Nashville, Tennessee.

Section on Railway Surgery—Dr. J. W. Palmer, Chairman, Ailey, Georgia; Dr. Edward V. Milholland, Vice-Chairman, Baltimore, Maryland; Dr. George A. Traylor, Secretary, Augusta, Georgia.

Section on Ophthalmology and Otolaryngology—Dr. Grady E. Clay, Chairman, Atlanta, Georgia; Dr. Oscar M. Marchman, Vice-Chairman, Dallas, Texas; Dr. John R. Hume, Secretary, New Orleans, Louisiana.

Section on Medical Education—Dr. C. C. Bass, Chairman, New Orleans, Louisiana; Dr. Stuart Graves, Vice-Chairman, University, Alabama; Dr. Harvey S. Thatcher, Secretary, Little Rock, Arkansas.

Section on Public Health—Dr. T. H. D. Griffitts, Chairman, Savannah, Georgia; Dr. W. B. Grayson, Vice-Chairman, Little Rock, Arkansas; Dr. W. C. Williams, Secretary, Nashville, Tennessee.

American Public Health Association, Southern Branch (meeting conjointly with Southern Medical Association)—Dr. Victor H. Bassett, President, Savannah, Georgia; Mr. E. S. Tisdale, First Vice-President, Charleston, West Virginia; Miss Pearl McIver, Second Vice-President, Washington, D. C.; Dr. Fred W. Caudell, Third Vice-President, Louisville, Kentucky; Dr. G. Foard McGinnes, Secretary-Treasurer, Richmond, Virginia.

National Malaria Committee (meeting conjointly with Southern Medical Association)—Dr. L. O. Howard, Honorary Chairman, Washington, D. C.; Dr. W. V. King, Chairman, Orlando, Florida; Dr. T. H. D. Griffitts, Chairman-Elect, Savannah, Georgia; Mr. L. M. Clarkson, Vice-Chairman, Atlanta, Georgia; Dr. Mark F. Boyd, Secretary-Treasurer, Tallahassee, Florida.

American Society of Tropical Medicine (meeting conjointly with Southern Medical Association)—Dr. Herbert C. Clark, President, Panama. R. de P.; Dr. Mark F. Boyd, President-Elect, Tallahassee, Florida; Dr. Karl F. Meyer, Vice-President, San Francisco, California; Dr. N. Paul Hudson, Secretary-Treasurer, Columbus, Ohio; Dr. Charles F. Craig, Editor, New Orleans, Louisiana.

Allergy Clinic and Round Table (meeting conjointly with Southern Medical Association)—Dr. J. Harvey Black, Chairman, Dallas, Texas; Dr. Oscar Swineford, Jr., Vice-Chairman, Charlottesville, Virginia; Dr. Charles H. Eyermann, Secretary, St. Louis, Missouri.

Society for Experimental Biology and Medicine, Southern Section (meeting conjointly with Southern Medical Association)—Dr. Roy H. Turner, President, New Orleans, Louisiana; Dr. Alton Ochsner, Vice-President, New Orleans, Louisiana; Dr. H. S. Mayerson, Secretary, New Orleans, Louisiana.

Southern Association of Anesthetists (meeting conjointly with Southern Medical Association)—Dr. Joseph McNearney, President, Maplewood, Missouri; Dr. Eldon B. Tucker, President-Elect, Morgantown, West Virginia; Dr. Joseph P. Bogan, Vice-President, Washington, D. C.; Dr. Wm. Hamilton Long, Secretary-Treasurer, Louisville, Kentucky.

American Academy of Pediatrics, Region 2 (meeting conjointly with Southern Medical Association)—Dr. Edward Clay Mitchell, Chairman, Memphis, Tennessee.

Women Physicians of the Southern Medical Association—Dr. Leta J. White, Chairman, Petersburg, Virginia; Dr. Regena C. Beck, Vice-Chairman, Richmond, Virginia; Dr. Edna S. Pennington, Secretary, Nashville, Tennessee; Dr. Lillian H. South, Historian, Louisville, Kentucky.

Woman's Auxiliary to the Southern Medical Association—Mrs. Frank N. Haggard, President, San Antonio, Texas; Mrs. Luther Bach, President-Elect, Bellevue, Kentucky; Mrs. W. K. West, First Vice-President, Oklahoma City, Oklahoma; Mrs. W. T. Wootton, Second Vice-President, Hot Springs, Arkansas; Mrs. R. H. Clark, Recording Secretary, Hattiesburg, Mississippi; Mrs. H. O. Wyneken, Corresponding Secretary, San Antonio, Texas; Mrs. Chas. P. Corn, Treasurer, Greenville, South Carolina; Mrs. B. S. Preston, Historian, Charleston, West Virginia; Mrs. Olin S. Cofer, Parliamentarian, Atlanta, Georgia.

BOOK REVIEWS continued from page 561

The Diagnosis and Treatment of Diseases of the Stomach and Intestines. By William Fitch Cheney, B.L., M.D., Clinical Professor of Medicine (Emeritus), Stanford University Medical School; Formerly Professor of Principles and Practice of Medicine, Cooper Medical College, San Francisco, California. Henry A. Christian, M.D., Sc.D., LL.D., General Editor of the Series. (Reprinted from Oxford Monographs on Diagnosis and Treatment.) 378 pages. New York: Oxford University Press, 1937. Cloth, $5.50.

This book is a comprehensive discussion of diagnosis and treatment of the various groups of gastro-intestinal diseases. The style is unique in that each chapter opens with a table of contents and a systematic outline of method of diagnosis and treatment follows, with case reports inserted. Lengthy theoretical discussions are avoided; simplicity in outlining the present knowledge of the subject is the keynote, resulting in easily accessible information that will be of practical value to its readers.

Southern Medical News

ST. LOUIS CLINICS SPRING CONFERENCE

The St. Louis Clinics will hold its Annual Spring Conference this year from May 24 to 29. Clinical demonstrations will be given daily beginning at nine o'clock each morning and ending at five in the evening. The final program has been placed in the mails and a perusal of it shows that there will be seventy-five demonstrations during the six-day period. The subjects are diversified and cover all the various branches of medicine with emphasis being given to those problems which confront the general practitioner. The teaching facilities of both universities, as well as those of the various hospital staffs in St. Louis, will be utilized during this conference. All demonstrations will be well organized and given with dispatch. Many of the members of the Southern Medical Association have been mailed programs. Those who did not receive a program and are desirous of obtaining further information may obtain same by addressing the Secretary, St. Louis Clinics, 3839 Lindell Blvd., St. Louis.

ALABAMA

The Alabama State Medical Association met in Birmingham April 20-22.

Dr. Thomas Earle Martin, Guntersville, and Miss Celia Dean were married in February.

Deaths

Dr. W. D. Stickley, Fairfield, aged 39, died April 12.

Dr. Joseph Manning Steiner, Greenville, aged 56, died recently of an injury received in a fall.

Dr. Samuel Kirkpatrick, Selma, aged 71, died January 6 of heart disease.

Dr. Henry Tutwiler Young, Greensboro, aged 67, died recently of acute dilatation of the heart and myocarditis.

Dr. Thomas Quincy Ray, Andalusia, aged 71, died January 3 of cerebral hemorrhage and hypertension.

Dr. Drury Orestes McCrary, Mobile, aged 67, died January 22 of hypertrophy of the prostate.

Dr. Thomas Smith, Eutaw, aged 65, died March 21.

Dr. R. B. Warren, Deatsville, aged 63, died March 17.

Dr. A. D. Killian, Alberta City, aged 66, died March 20.

ARKANSAS

The State Board of Health has elected the following officers for the coming year: Dr. Fergus O. Mahony, El Dorado, President; Dr. Melvin E. McCaskill, Little Rock, Vice-President.

The Davis Hospital Staff, Pine Bluff, has elected the following officers for the coming year: Dr. Virgil Payne, President; Dr. C. B. Capel, Vice-President; Dr. Ross Maynard, Secretary.

Dr. F. H. Krock, Fort Smith, has been made Chairman of the Red Cross Chapter of Sebastian County.

Dr. S. A. Thompson, Camden, was recently made a Trustee of the Henderson State Teachers' College.

Dr. A. C. Watson, England, has been made Superintendent of the Benton Farm Colony of the State Hospital.

Dr. Thomas C. Watson, Benton, has been made Medical Director of Saline, Hot Springs and Grant Counties.

Dr. C. J. Steed, Gurdon, has been elected Governor of the Board of Trade of that city.

Deaths

Dr. Cicers Camp, Patmos, aged 66, died recently.

Dr. George Eric Miller, Fayetteville, aged 84, died recently.

Dr. Horace Rudolph McCarroll, Walnut Ridge, aged 65, died March 3.

Dr. Ernest Glyndon Epler, Fort Smith, aged 76, died February 22.

Dr. James M. Williams, Malvern, aged 82, died March 17.

DISTRICT OF COLUMBIA

Dr. Lewis Harvie Taylor, Washington, has been made President of the Visiting Staff of Sibley Memorial Hospital.

Dr. James G. Townsend, Washington, has been made President of the Tuberculosis Association of the District of Columbia to succeed Dr. William C. White.

Deaths

Dr. Isaiah Alpheus Boyd, Washington, aged 71, died January 23 of pneumonia.

Dr. William Alanson White, Washington, aged 67, died March 7 of pneumonia and influenza.

Dr. Alexander Fitzhugh Magruder, Washington, aged 87, died January 27 of pneumonia.

FLORIDA

The Alachua County Medical Society has elected the following officers for the coming year: Dr. T. A. Snow, Gainesville, President; Dr. J. E. Maines, Sr., Gainesville, First Vice-President; Dr. R. E. Summitt, Gainesville, Second Vice-President; Dr. H. M. Merchant, Gainesville, Secretary-Treasurer.

The Columbia County Medical Society has elected the following officers for the coming year: Dr. Thomas H. Bates, Lake City, President; Dr. W. S. Nichols, Lake City, Vice-President; Dr. M. W. Spearman, Lake City, Secretary-Treasurer.

The Bay County Medical Society has elected the following officers for the coming year: Dr. D. M. Adams, Panama City, President; Dr. W. J. Blackshear, Panama City, Vice-President; Dr. A. H. Miller, Millville, Secretary-Treasurer.

The Lake County Medical Society has elected the following officers for the coming year: Dr. L. H. Oetjen, Leesburg, President; Dr. H. T. Fenn, Mt. Dora, Vice-President; Dr. W. L. Ashton, Umatilla, Secretary-Treasurer.

The Lee County Medical Society has elected the following officers for the coming year: Dr. H. Quillian Jones, Fort Myers, President; Dr. Baker Whisnant, Fort Myers, Vice-President; Dr. Harvie J. Stipe, Fort Myers, Secretary-Treasurer.

The Leon-Gadsden-Liberty-Wakulla-Jefferson County Medical Society has elected the following officers for the coming year: Dr. L. L. Dozier, Tallahassee, President; Dr. W. D. Rogers, Chattahoochee, Vice-President; Dr. B. A. Wilkinson, Tallahassee, Secretary-Treasurer.

The Palm Beach County Medical Society has elected the following officers for the coming year: Dr. Bailey B. Sory, Jr., West Palm Beach, President; Dr. Wilbur O. Arnold, West Palm Beach, Vice-President; Dr. Lloyd J. Netto, West Palm Beach, Secretary; Dr. F. K. Herpel, West Palm Beach, Treasurer.

The St. Johns County Medical Society has elected the following officers for the coming year: Dr. C. C. Grace, St. Augustine, President; Dr. W. D. Webb, St. Augustine, Vice-President; Dr. R. D. Harris, St. Augustine, Secretary; Dr. A. C. Walkup, St. Augustine, Treasurer.

The Volusia County Medical Society has elected the following officers for the coming year: Dr. J. Ralston Wells, Daytona Beach, President; Dr. Hugh West, DeLand, Vice-President; Dr. R. L. Miller, Daytona Beach, Secretary-Treasurer.

The St. Lucie-Okeechobee-Indian River-Martin County Medical Society has elected the following officers for the coming year: Dr. H. D. Clark, Fort Pierce, President; Dr. R. C. Boothe, Fort Pierce, Vice-President; Dr. Grover C. Hardie, Fort Pierce, Secretary-Treasurer.

Dr. Alfred T. Eide, Lake Placid, has been made a member of the House of Representatives of the State Legislature.

Dr. Frank L. Quillman, formerly of Winter Garden, has been made Health Officer of Orange County with offices in Orlando.

Dr. William G. Doen, Daytona Beach, is in Milwaukee doing research work.

Dr. H. J. Blackmon, Tampa, has returned after studying in Philadelphia.

Dr. Cornelius S. Franckle, St. Petersburg, and Miss Ruth Travers were married recently.

Dr. Lewis William Glatzau and Mrs. Winnifred McDonald, both of Daytona Beach, were married recently.

Deaths

Dr. J. M. Grantham, Tampa, aged 64, died February 26.

Dr. Joseph Henderson Coffee, Arcadia, aged 58, died January 25 of influenza and pneumonia.

Dr. Francisco Maria y Hernandez Fernandez, Miami, aged 50, died February 14 of coronary thrombosis and diabetes mellitus.

Dr. Horace Lindsley, St. Augustine, aged 81, died January 21 of carcinoma of the descending colon.

Dr. Zeno Burt Babbitt, St. Petersburg, aged 75, died February 3.

GEORGIA

The Ben Hill County Medical Society has elected the following officers for the coming year: Dr. R. M. Ware, Fitzgerald, President; Dr. W. P. Coffee, Fitzgerald, Vice-President; Dr. L. S. Osborne, Fitzgerald, Secretary-Treasurer.

The Cobb County Medical Society has elected the following officers for the coming year: Dr. W. C. Mitchell, Smyrna, President; Dr. H. B. Terry, Acworth, Vice-President; Dr. J. E. Lester, Marietta, Secretary-Treasurer.

The Dooly County Medical Society has elected the following officers for the coming year: Dr. V. L. Harris, Pinehurst, President; Dr. M. L. Malloy, Vienna, Vice-President.

The Fulton County Medical Society has elected the following officers for the coming year: Dr. H. Cliff Sauls, Atlanta, President; Dr. C. C. Aven, Atlanta, President-Elect; Dr. J. Harry Rogers, Atlanta, Vice-President; Dr. M. T. Harrison, Atlanta, Secretary-Treasurer.

The Gordon County Medical Society has elected the following officers for the coming year: Dr. W. R. Barnett, Calhoun, President; Dr. Z. V. Johnston, Calhoun, Secretary-Treasurer.

The Hancock County Medical Society has elected the following officers for the coming year: Dr. Horace Darden, Sparta, President; Dr. H. L. Earl, Sparta, Secretary-Treasurer.

The Jefferson County Medical Society has elected the following officers for the coming year: Dr. J. D. Peacock, Wadley, President; Dr. John J. Pilcher, Wrens, Vice-President; Dr. S. T. R. Revell, Louisville, Secretary-Treasurer.

The Meriwether and Harris County Medical Society has elected the following officers for the coming year: Dr. V. H. Bennett, Gay, President; Dr. W. P. Allen, Woodbury, Vice-President; Dr. R. B. Gilbert, Greenville, Secretary-Treasurer.

The Polk County Medical Society has elected the following officers for the coming year: Dr. Seale L. Whitley, Cedartown, President; Dr. Charles V. Wood, Cedartown, Vice-President; Dr. John M. McGehee, Cedartown, Secretary-Treasurer.

The Rockdale County Medical Society has elected the following officers for the coming year: Dr. P. S. Smith, Conyers, President; Dr. S. A. Ware, Conyers, Vice-President; Dr. H. E. Griggs, Conyers, Secretary-Treasurer.

The Warren County Medical Society has elected the following officers for the coming year: Dr. H. B. Cason, Jr., Warrenton, President; Dr. A. W. Davis, Warrenton, Secretary-Treasurer.

The Washington County Medical Society has elected the following officers for the coming year: Dr. O. D. Lennard, Tennille, President; Dr. S. B. Malone, Sandersville, Vice-President; Dr. W. M. Cason, Sandersville, Secretary-Treasurer.

The Whitfield County Medical Society has elected the following officers for the coming year: Dr. J. H. Steed, Dalton, President; Dr. G. L. Broaddrick, Dalton, Vice-President; Dr. H. J. Ault, Dalton, Secretary-Treasurer.

The Wilkes County Medical Society has elected the following officers for the coming year: Dr. C. E. Wills, Washington, President; Dr. H. M. Sale, Sharon, Vice-President; Dr. A. W. Simpson, Washington, Secretary-Treasurer.

The St. Joseph Infirmary Staff, Atlanta, has elected the following officers for the coming year: Dr. W. C. Waters, President; Dr. Stephen T. Barnett, Jr., Vice-President; Dr. Don F. Cathcart, Secretary.

Dr. V. C. Daves and Dr. M. L. Malloy, Vienna, have been made members of the Vienna Board of Health.

The Grady Hospital Staff, Atlanta, has elected the following officers for the coming year: Dr. Dan C. Elkin, President; Dr. Thomas P. Goodwyn, Vice-President; Dr. C. W. Strickler, Jr., Secretary-Treasurer.

Dr. T. Sterling Claiborne, Atlanta, has opened offices in the Medical Arts Building.

Dr. John A. Simpson, Athens, and Miss Mary Louise Schuman were married recently.

Deaths

Dr. William Richard Moore, Cairo, aged 70, died January 8 of influenza.

Dr. Lee Bird, Rock Spring, aged 59, died January 11 of cardiovascular renal disease.

Dr. John Jackson Johnson, Calhoun, aged 29, died January 9 of injuries received in an automobile accident.

Dr. Robert L. Z. Bridges, Brinson, aged 66, died February 14.

Dr. William Richard Moore, Cairo, aged 70, died January 8 of influenza.

Dr. Thomas J. McArthur, Cordele, aged 68, died February 15 of heart disease.

Dr. Joseph H. Hand, Blakely, aged 81, died February 4.

Dr. Benjamin Frederick Preston, Farmington, aged 60, died February 3.

Dr. Roscoe Felix Johnson, Columbus, aged 45, died January 31 of heart disease.

KENTUCKY

Dr. Thomas H. Milton, Kenvir, and Miss Alice Kammeyer were married in February.

Deaths

Dr. E. Lafayette Harmon, Corbin, aged 56, died January 19 of cerebral hemorrhage.

Continued on page 32

The UNIVERSITY of MARYLAND SCHOOL of MEDICINE

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X-RAY—Practical instruction in fluoroscopy and the interpretation of films. Fee, $50.00. Dr. C. C. McClure.

* These courses require a minimum enrollment of five. Applications must be made one week in advance, accompanied by a deposit of $5.00, which will be returned if the course is not given.

JUNE 28-JULY 17

ALLERGY—Three weeks of practical and clinical instruction in the diagnosis and treatment of allergic diseases, including the preparation and standardization of extracts. Fee, $50.00. Drs. Edna Pennington and Clarence Thomas.

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* These courses require a minimum enrollment of ten and four each. Applications must be made one week in advance, accompanied by a deposit of $5.00, which will be returned if the course is not given.

For Further Information, Address the Registrar

VANDERBILT UNIVERSITY MEDICAL SCHOOL
NASHVILLE, TENNESSEE

Continued from page 564

Dr. James M. Digby, Newport, aged 70, died January 17 of heart disease.

Dr. Mary Carswell McClellan, Lexington, aged 63, died recently.

Dr. James Dallas Liles, Vanceburg, aged 55, died January 16.

Dr. Charles Hunt, Clinton, aged 62, died January 24.

Dr. Robert L. Cherry, Bardstown, aged 76, died January 2.

Dr. Parvin Douglas Gillim, Owensboro, aged 55, died April 2 of heart disease.

LOUISIANA

The Ascension Parish Medical Society has elected the following officers for the coming year: Dr. D. C. Brumfield, Darrow, President; Dr. H. A. Folse, Donaldsonville, Vice-President; Dr. Myer Epstein, Gonzales, Secretary-Treasurer.

The Calcasieu Parish Medical Society has elected the following officers for the coming year: Dr. T. C. Moody, Lake Charles, President; Dr. Walter Moss, Lake Charles, Vice-President; Dr. Eleanor Cook, Lake Charles, Secretary-Treasurer.

The Concordia-Catahoula-Bi-Parish Medical Society has elected the following officers for the coming year: Dr. H. H. Ratcliffe, Ferriday, President; Dr. J. P. Durham, Jonesville, Vice-President; Dr. John Schreiber, Vidalia, Secretary-Treasurer.

The East and West Feliciana Bi-Parish Medical Society has elected the following officers for the coming year: Dr. S. L. Shaw, Clinton, President; Dr. W. J. Roberts, Felixville, Vice-President; Dr. E. M. Toler, Clinton, Secretary-Treasurer.

The Morehouse Parish Medical Society has elected the following officers for the coming year: Dr. W. W. Poimboeuf, Bastrop, President; Dr. J. N. Jones, Bastrop, Vice-President; Dr. F. B. Ogden, Bastrop, Secretary-Treasurer.

The Rapides Parish Medical Society has elected the following officers for the coming year: Dr. I. N. Adams, Pineville, President; Dr. A. J. Morat, Colfax, First Vice-President; Dr. O. B. Owens, Alexandria, Second Vice-President; Dr. M. B. Pearce, Alexandria, Secretary.

The St. Mary Parish Medical Society has elected the following officers for the coming year: Dr. J. T. Prosser, Morgan City, President; Dr. Ford S. Williams, Franklin, Secretary-Treasurer.

The Shreveport Medical Society has elected the following officers for the coming year: Dr. W. B. Heidon, Shreveport, President; Dr. R. T. Lucas, Shreveport, First Vice-President; Dr. W. J. Sandidge, Shreveport, Second Vice-President; Dr. P. D. Abramson, Shreveport, Secretary; Dr. D. R. McIntyre, Shreveport, Treasurer.

The Terrebonne Parish Medical Society has elected the following officers for the coming year: Dr. R. W. Collins, Houma, President; Dr. J. B. Duval, Houma, Vice-President; Dr. S. F. Landry, Houma, Secretary-Treasurer.

The Washington Parish Medical Society has elected the following officers for the coming year: Dr. J. S. Desporte, Bogalusa, President; Dr. A. F. Adair, Bogalusa, Vice-President; Dr. F. A. Williams, Franklinton, Secretary-Treasurer.

Dr. Charles M. McGill, formerly of Boston, Massachusetts, has moved to New Orleans.

Dr. Seth A. McConnell, formerly of Jackson, has moved to Houston, Texas.

DEATHS

Dr. Edward Larned McGehee, Jr., Hammond, aged 57, died January 30 of hypertensive heart disease and nephritis.

Dr. William Davis Wall, Jr., Zachary, aged 66, died January 6 of angina pectoris.

MARYLAND

Dr. Adolph Weinzirl, formerly of the Baltimore City Health Department, has been made Health Officer of the City of Portland, Oregon.

Dr. Lowell J. Reed, Professor of Biostatistics of Johns Hopkins School of Hygiene and Public Health has been made Dean of the School, succeeding Dr. Allen W. Freeman.

Dr. James L. Gamble, Boston, Massachusetts, will deliver the William Sydney Thayer and Susan Read Thayer Lectureship at Johns Hopkins University School of Medicine.

Dr. Maurice L. Townsend, Chevy Chase, and Miss Nell Hamlin were married February 25.

DEATHS

Dr. Randolph Winslow, Baltimore, aged 84, died February 27.

Dr. Warren Daniel Miller, Hagerstown, aged 56, died January

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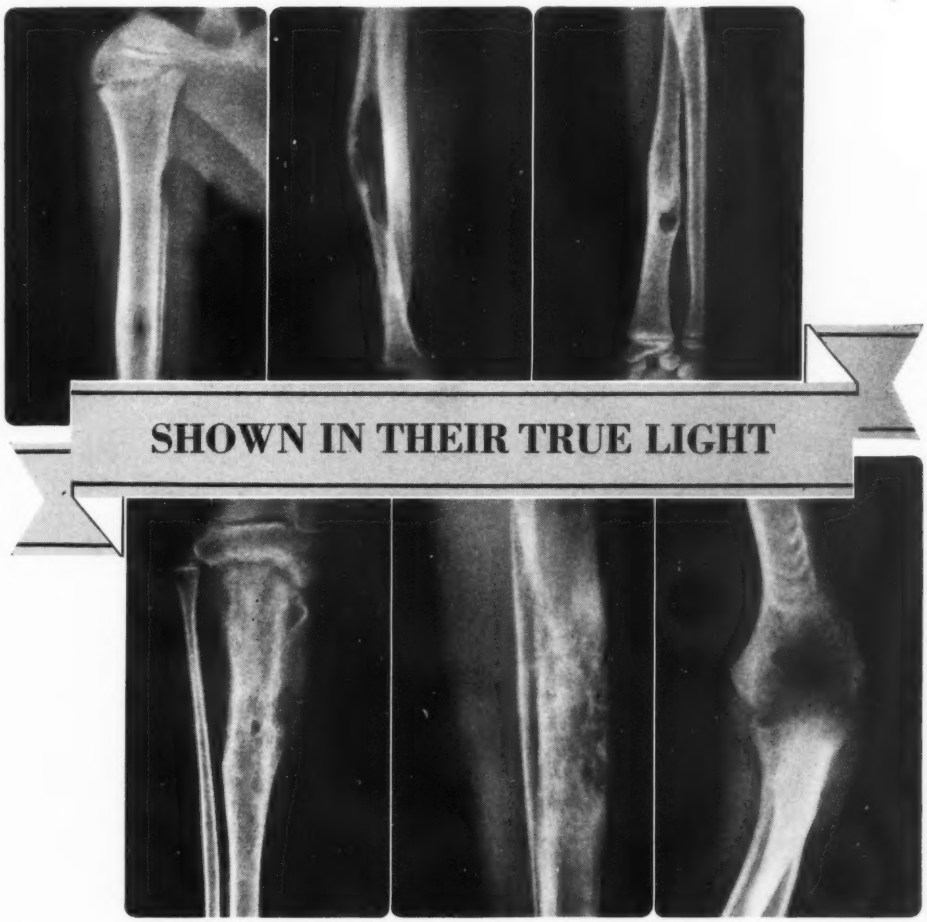

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PEDIATRICS

July 1-31. Fee, $125.

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For further information regarding the above courses apply to the
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DEAN GRADUATE SCHOOL OF MEDICINE

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New Orleans, La.

Continued from page 32

16 of carcinoma of the transverse colon, perforation of the colon and peritonitis.

Dr. John E. O'Neill, Henryton, aged 62, died recently of uremia and coronary thrombosis.

Dr. David W. Jones, Baltimore, aged 74, died January 17 of myocarditis.

Dr. Roy Verner Heuver, Middletown, aged 62, died January 18 of coronary thrombosis.

Dr. Bernard Joseph Wess, Baltimore, aged 54, died January 8 of coronary thrombosis.

Dr. Charles S. Parker, Baltimore, aged 79, died January 25 of chronic myocarditis.

MISSISSIPPI

The DeSoto County Medical Society has elected the following officers for the coming year: Dr. J. M. Wright, Hernando, President; Dr. H. M. Wadsworth, Hernando, Vice-President; Dr. L. L. Minor, Memphis, Tennessee, Secretary-Treasurer.

The Homochitto Valley Medical Society has elected the following officers for the coming year: Dr. Harrison Butler, Liberty, President; Dr. W. T. Thornhill, Crosby, Dr. Edwin Benoist, Natchez, Dr. C. E. Mullins, Bude, Dr. R. B. Harper, Fayette, Dr. Charles Catchings, Woodville, Vice-Presidents; Dr. H. A. Whittington, Natchez, Secretary-Treasurer.

Dr. Robert M. Moore, Assistant Professor of Pathology, University of Missouri School of Medicine, Columbia, has been made Professor of Pathology and Director of Clinical Laboratory Diagnosis at the University of Mississippi School of Medicine, to take over his duties on September 1.

Dr. E. W. Green, formerly of Longview, Texas, announces his association with Dr. B. S. Guyton, Oxford.

DEATHS

Dr. James B. Dudley, Utica, aged 76, died recently.

Dr. John Bommer, Midnight, aged 94, died January 30.

Dr. W. V. Davis, Booneville, aged 75, died March 7.

MISSOURI

The American College of Physicians met in St. Louis April 19-23.

The Missouri Public Health Association met in Springfield April 29-30.

The State Board of Health has elected the following officers for the coming year: Dr. Edward S. Smith, Kirksville, President; Dr. Walter L. Brandon, Poplar Bluff, Vice-President.

The Missouri Chapter of the National Society for the Advancement of Gastroenterology has elected the following officers for the coming year: Dr. Horace W. Soper, St. Louis, President; Dr. Frank D. Gorham, St. Louis, Vice-President; Dr. Charles W. Duden, St. Louis, Secretary; Dr. Lee Pettit Gay, St. Louis, Treasurer.

Dr. John R. Caulk, St. Louis, has been made Vice-President of the American Association of Clinical Genito-Urinary Surgeons.

Dr. Alexis F. Hartman, St. Louis, has been made Professor of Pediatrics at Washington University School of Medicine and Physician-in-Chief to St. Louis Children's Hospital, succeeding the late Dr. W. McKim Marriott.

The St. Louis County Hospital Staff has elected the following officers for the coming year: Dr. Fred W. Bailey, Chief of Staff; Dr. Leo Will, Vice-Chief; Dr. O. P. Hampton, Secretary.

Dr. Evarts A. Graham, St. Louis, has received the John Scott Award consisting of a medal and $1,000 in recognition of his application of the roentgen ray in the study and diagnosis of gallbladder conditions.

Dr. Frederick E. Rose and Miss Felicia Green, both of St. Louis, were married in January.

DEATHS

Dr. John James Millman, Florissant, aged 64, died January 10 of heart disease, arteriosclerosis and hypertension.

Dr. James Larkin Craig, Webb City, aged 53, died January 12 of agranulocytic angina.

Dr. John H. Holke, St. Louis, aged 75, died recently.

Dr. Elmer Logan Sloan, Joplin, aged 67, died recently.

Dr. Ross A. Mitchell, Moberly, aged 55, died recently of myocarditis.

Dr. Alpheus Luther Pollard, Sedalia, aged 81, died January 2 of essential hypertension and hemiplegia.

Dr. Albert Hawes Cordier, Kansas City, aged 78, died January 23 of pneumonia.

Continued on page 36

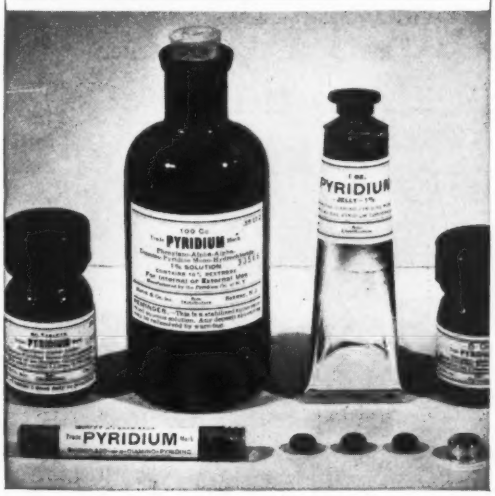
CLINICAL EXPERIENCES WITH TRADE PYRIDIUM MARK IN

CYSTITIS

PYELITIS
(PYELONEPHRITIS)

PROSTATITIS

URETHRITIS



CYSTITIS

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PYELITIS
(PYELONEPHRITIS)

"The prompt effect this drug exerts upon bacterial growth in urinary tract infections, as well as in those in contiguous structures, must be seen to be appreciated."

PROSTATITIS

"In a series of fifty-three cases of chronic prostatitis, we have found that pyridium taken internally, plus massage of the prostate gland, greatly reduces the period of treatment."

URETHRITIS

"It will be noted that the course of the treatment was markedly lessened over the time needed with methods which we formerly used. The average duration of our control group was 109 days and for the pyridium group 71 days. Also, in our experience in these and other cases, the development of complications was demonstrated to be less frequent when pyridium was employed."

• *Quoted from published clinical reports.*

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Continued from page 34

Dr. John Paul Hoeffer, St. Louis, aged 69, died January 24 of coronary occlusion.

Dr. William B. Shields, St. Louis, aged 73, died January 22 of pneumonia.

Dr. Emanuel D. Block, Webster Groves, aged 81, died January 19 of chronic myocarditis and arteriosclerosis.

Dr. H. S. Forgrave, St. Joseph, aged 63, died February 14 of a blood clot resulting from an infected foot.

Dr. Edwin Elgin Evans, Columbia, aged 68, died February 8 of coronary thrombosis.

NORTH CAROLINA

The North Carolina Society for Mental Hygiene has elected the following officers for the coming year: Dr. Ernest R. Groves, Chapel Hill, President; Dr. Harry W. Crane, Durham, Secretary.

Dr. Julian W. Ashby, Raleigh, has been made President of the North Carolina Neuro-Psychiatric Association.

Dr. Hillis L. Seay, Huntersville, has been made Superintendent of Mecklenburg Sanatorium.

Dr. Murray P. Whichard, Edenton, has been made Health Officer of Chowan County.

Dr. W. Raleigh Parker, Woodland, has been made Health Officer of Northampton County, succeeding Dr. H. M. Seawell.

Dr. R. M. Bardin, Rutherfordton, has been made Health Officer of Richmond County to succeed Dr. B. B. Dalton.

Dr. John Donnelly, Charlotte, has opened offices on North Tryon Street.

Dr. Otis Hunter Jones, Charlotte, has opened offices on West Seventh Street for the practice of obstetrics.

Dr. Raymond Harris Harmon and Miss Cleta Eufola Jones, both of Boone, were married January 31.

Dr. Carroll Bracey Robertson and Miss Mary Elizabeth Peebles, both of Jackson, were married February 27.

Dr. Jesse Burns Earle, Siler City, and Miss Helen Christine Pleasants were married recently.

Dr. Merle Dumont Bonner, Jamestown, and Miss Blanche Baker Hanff were married January 30.

Dr. Weldon Paul Sanger, Durham, and Miss Mary Ann Carr were married recently.

Dr. Clarence Paul Cameron, Fayetteville, and Miss Vivian Lebo were married recently.

DEATHS

Dr. Walter Olin Nisbet, Charlotte, aged 70, died January 18 of coronary occlusion.

Dr. G. F. Duncan, Sparta, aged 62, died February 27 of injuries received in an automobile accident.

OKLAHOMA

The Harmon County Medical Society has elected the following officers for the coming year: Dr. William G. Husband, Hollis, President; Dr. Russell H. Lynch, Hollis, Secretary.

Dr. William K. Ishmael, Oklahoma City, announces his association with the McBride Clinic and Reconstruction Hospital.

Dr. R. Keyes has moved from Okemah to Wewoka.

Dr. Jess Bird has moved from Altus to Oklahoma City.

Dr. R. M. Adams has moved from Hobart to Oklahoma City.

DEATHS

Dr. Bascomb B. Dawson, Ada, aged 62, died recently.

Dr. Charles Fleetwood House, Walters, aged 64, died January 8.

Dr. Charles T. Harris, Kiowa, aged 67, died February 7.

SOUTH CAROLINA

The Edisto Medical Society has elected the following officers for the coming year: Dr. M. L. Nelson, North, President; Dr. A. W. Lowman, Denmark, Vice-President; Dr. H. M. Eargle, Orangeburg, Secretary-Treasurer.

The Greenwood County Medical Society has elected the following officers for the coming year: Dr. W. J. Holloway, President; Dr. B. H. Morgan, Vice-President; Dr. J. M. Symmes, South Greenwood, Secretary.

Dr. John K. Stuhvey, Jr., Conway, and Miss Charlotte Barbara Reynolds were married in December.

Continued on page 38

THE NEW YORK POLYCLINIC
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Continued from page 36

DEATHS

Dr. Robert Hamilton Folk, Belton, aged 48, died January 17 of bronchopneumonia and myocarditis.

Dr. Ephraim W. Ellis, Dunbarton, aged 74, died January 3 of hypertrophy of the prostate and bronchopneumonia.

Dr. James Mauly Brown, McCormick, aged 59, died January 11.

TENNESSEE

The Tennessee State Medical Association met in Knoxville April 13-15.

The Tennessee State Pediatric Association has elected the following officers for the coming year: Dr. Eugene Rosamond, Memphis, President; Dr. William E. Vanorder, Chattanooga, Vice-President; Dr. Kinsey M. Buck, Memphis, Secretary-Treasurer.

Dr. William Allison Stem, Chattanooga, and Miss Mary Lucille Converse were married in December.

Dr. Joseph Thomas Whitfield and Miss Virginia Louise Evans, both of Nashville, were married recently.

DEATHS

Dr. Ira Jackson Tatum, Union City, aged 71, died January 4 of coronary occlusion.

Dr. Duncan Eve, Sr., Nashville, aged 84, died February 15 of senility.

Dr. Charles Kincaid Summers, Nashville, aged 58, died January 28 of pneumonia.

Dr. Joseph A. Lipscomb, Memphis, aged 93, died February 23.

TEXAS

The Texas Radiological Society has elected the following officers for the coming year: Dr. E. V. Powell, Temple, President; Dr. Jerome Smith, San Angelo, First Vice-President; Dr. C. F. Carin, Corpus Christi, Second Vice-President; Dr. Matt Glover, Wichita Falls, Secretary-Treasurer.

The Texas Society for Mental Hygiene has elected the following officers for the coming year: Dr. E. M. Perry, Dallas, President; Dr. T. W. Buford, Minter, Vice-President; Rev. James S. Allen, Austin, Secretary; Dr. Wilmer L. Allison, Fort Worth, Treasurer.

The South Texas Postgraduate Assembly has elected the following officers for the coming year: Dr. J. Harolde Turner, Houston, President; Dr. H. H. Loos, Bay City, Dr. George Sladczyk, Port Arthur, Dr. H. Reid Robinson, Galveston, Vice-Presidents; Dr. Robert T. Haynes, Houston, Secretary; Dr. Byron P. York, Houston, Treasurer.

The Baylor-Knox-Haskell Counties Medical Society has elected the following officers for the coming year: Dr. T. W. Williams, Haskell, President; Dr. R. L. Newsom, Munday, Vice-President; Dr. J. W. Foy, Seymour, Secretary.

The Galveston County Medical Society has elected the following officers for the coming year: Dr. J. L. Jinkins, Galveston, President; Dr. J. R. McMurray, Galveston, Vice-President; Dr. Francis A. Garbade, Galveston, Secretary-Treasurer.

The Falls County Medical Society has elected the following officers for the coming year: Dr. L. C. Carter, Marlin, President; Dr. C. F. Miller, Marlin, Vice-President; Dr. Walter S. Smith, Marlin, Secretary.

Continued on page 40

THE JEFFERSON MEDICAL COLLEGE of PHILADELPHIA

THE ONE HUNDRED AND THIRTEENTH ANNUAL SESSION BEGINS SEPTEMBER 20, 1937, AND ENDS JUNE 3, 1938.

FOUNDED 1825. A Chartered University Since 1838. Graduates number 16,175.

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MEMBER OF HOSPITAL EXHIBITORS ASS'N.

Continued from page 38

The Hamilton County Medical Society has elected the following officers for the coming year: Dr. H. V. Hedges, Hico, President; Dr. John Talley, Hamilton, Vice-President; Dr. R. A. Kooken, Hamilton, Secretary-Treasurer.

The Lampasas County Medical Society has elected the following officers for the coming year: Dr. John W. Ellis, Lampasas, President; Dr. W. M. Brook, Lampasas, Vice-President; Dr. W. V. Bessonnette, Sanatorium, Secretary-Treasurer.

The Palo Pinto County Medical Society has elected the following officers for the coming year: Dr. C. R. Williams, Mineral Wells, President; Dr. W. B. Lasater, Mineral Wells, Vice-President; Dr. E. F. Yeager, Mineral Wells, Secretary-Treasurer.

The Potter County Medical Society has elected the following officers for the coming year: Dr. E. A. Rowley, Amarillo, President; Dr. Neal Hall, Amarillo, Vice-President; Dr. J. B. White, Amarillo, Secretary-Treasurer.

The Stephens-Shackelford-Throckmorton Counties Medical Society has elected the following officers for the coming year: Dr. J. E. Harrell, Throckmorton, President; Dr. Grover C. Wood, Breckenridge, Vice-President; Dr. D. J. R. Youngblood, Breckenridge, Secretary-Treasurer.

The Tierra Blanco County Medical Society has elected the following officers for the coming year: Dr. Mayes Miller, Dimmitt, President; Dr. D. W. Clark, Vega, Vice-President; Dr. R. R. Wills, Hereford, Secretary.

The Tom Green Eight County Medical Society has elected the following officers for the coming year: Dr. W. L. Bush, San Angelo, President; Dr. F. T. McIntire, San Angelo, Vice-President; Dr. D. D. Wall, San Angelo, Secretary; Dr. J. B. McKnight, Sanatorium, Treasurer.

The Travis County Medical Society has elected the following officers for the coming year: Dr. C. M. Darnall, Austin, President; Dr. W. R. Houston, Austin, Vice-President; Dr. J. T. Robison, Austin, Secretary.

The Washington County Medical Society has elected the following officers for the coming year: Dr. C. E. Southern, Burton, President; Dr. H. O. Hodde, Brenham, Vice-President; Dr. H. L. Steinbach, Brenham, Secretary-Treasurer.

The Webb Zapata-Jim Hogg Counties Medical Society has elected the following officers for the coming year: Dr. Ruby South Lowry, Laredo, President: Dr. C. J. Gorman, Laredo, Vice-President; Dr. F. M. Canseco, Secretary-Treasurer.

The Wilbarger County Medical Society has elected the following officers for the coming year: Dr. Howard J. Reger, Vernon, President; Dr. J. J. Muirhead, Vernon, Vice-President; Dr. Robert C. Stokes, Vernon, Secretary-Treasurer.

The Young County Medical Society has elected the following officers for the coming year: Dr. V. O. Rosser, Jr., Graham, President; Dr. B. B. Griffin, Graham, Vice-President; Dr. J. O. Baker, Bryson, Secretary.

The Bethania Hospital Staff, Wichita Falls, has elected the following officers for the coming year: Dr. J. E. Kanatser, President; Dr. B. R. Collins, Vice-President; Dr. William Rosenblatt, Secretary; Dr. L. B. Holland, Assistant Secretary.

The City-County Hospital Staff, Fort Worth, has elected the following officers for the coming year: Dr. W. Porter Brown, Chairman; Dr. X. R. Hyde, Vice-Chairman.

The Hendrick Memorial Hospital Staff, Abilene, has elected the following officers for the coming year: Dr. J. M. Estes, Sr., President; Dr. C. L. Prichard, Vice-President; Dr. L. F. Johnson, Secretary.

The Hotel Dieu Hospital Staff, Beaumont, has elected the following officers for the coming year: Dr. T. L. Pecora, President; Dr. T. A. Fears, Vice-President; Dr. W. J. Graber, Secretary-Treasurer.

The Hotel Dieu Hospital Staff, El Paso, has elected the following officers for the coming year: Dr. Will P. Rogers, President; Dr. W. H. Stevenson, Secretary-Treasurer.

The Jefferson Davis Hospital Staff, Houston, has elected the following officers for the coming year: Dr. John M. Trible, President; Dr. Sidney Lister, Vice-President.

The McAllen Municipal Hospital Staff, McAllen, has elected the following officers for the coming year: Dr. M. Lyle Talbot, McAllen, Chairman; Dr. A. D. Wilson, Mission, Vice-Chairman; Dr. W. E. Whigham, McAllen, Secretary-Treasurer.

The Medical Arts Hospital Staff, Brownwood, has elected the following officers for the coming year: Dr. H. B. Allen, President; Dr. W. B. Anderson, Vice-President; Dr. J. M. Horn, Secretary.

The Methodist Hospital Staff, Dallas, has elected the follow-

Continued on page 42

BETTER THAN EVER!
KOMPAK MODEL
New Features
COMPLETE NEW DRESS—INSIDE AND OUT
Hard wear-resisting finish—opalescent gray, black and silver
TUBE MOUNTING CARELESSNESS-PROOF
Practically defies glass breakage. Facilitates exact reading
BEAUTIFUL MODERN SCALE
Platinum-like debossed numbers on black alumilited metal
SOLID ONE-PIECE DIE-CAST DURALUMIN
Light as aluminum—strong as steel.
AND MANY OTHER NEW FEATURES . . .
ALL THE EXCLUSIVE FEATURES THAT HAVE MADE THE BAUMANOMETER "STANDARD FOR BLOODPRESSURE THE WORLD OVER"
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40 times that of Phenol

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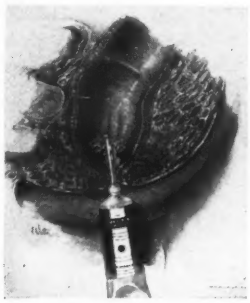

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Continued from page 40

ing officers for the coming year: Dr. Joe H. McGuire, President; Dr. Frank Selecman, Vice-President; Dr. Andrew Small, Secretary.

Dr. A. C. Scott, Jr., Temple, has been made Director of the Temple Chamber of Commerce and Board of Development.

Dr. John W. Brown, Austin, has been made City Health Officer of Houston.

Dr. H. S. Robertson, Linden, has been made Physician at the Eastham Prison Farm to succeed Dr. W. N. Dominey, resigned.

Dr. J. Alston Clapp, Jr., Houston, has opened offices in the Medical Arts Building.

Dr. C. M. Shumway, McKinney, has returned after taking postgraduate work in Chicago.

Dr. J. Edward Johnson, Mineral Wells, has returned after taking postgraduate work at Sanatorium.

Dr. M. E. Childers, San Antonio, is taking postgraduate work in Boston.

Dr. T. H. Cheavens, Dallas, has returned after taking postgraduate work in New York.

Dr. William M. Blair has moved from Little Rock, Arkansas, to Waco.

Dr. Robert L. Currie has moved from Houston to Lott.

Dr. J. W. Eschenbrenner has moved from Wichita Falls to Fort Worth.

Dr. Joe R. Gandy has moved from Lipan to Houston.

Dr. William M. Garner has moved from Longview to Atlanta.

Dr. John M. Hooper has moved from Fort Worth to Denton.

Dr. W. E. Huddleston has moved from Galveston to Taos, New Mexico.

Dr. G. W. Luckey has moved from Fort Worth to Austin.

Dr. J. S. McCreary has moved from Crockett to Buffalo.

Dr. C. F. Osborne has moved from Silsbee to Sherman.

Dr. Don C. Peterson has moved from Austin to Franklin, Tennessee.

Dr. Homer E. Prince has moved from Galveston to Houston.

Dr. H. S. Robertson has moved from Bivins to Weldon.

Dr. Charles W. Rudolph has moved from Fort Worth to Albuquerque, New Mexico.

Dr. C. A. Schaub has moved from Dallas to Wilson.

Dr. William M. Smith has moved from San Angelo to Midland.

Dr. William R. Stovall has moved from Tyler to Lufkin.

Dr. E. G. Ward has moved from Dallas to Wichita Falls.

Dr. George W. Wilhite has moved from Tyler to Willcox, Arizona.

Dr. Harriss Williams has moved from Galveston to Austin.

Dr. George M. Waddill, Jr., Amarillo, and Miss Esther Beeman were married February 6.

Dr. Craig Munter, Fort Worth, and Miss Elizabeth Coker were married February 3.

Dr. Norman D. Jarrell, Temple, and Miss Nannette E. Kahn were married February 15.

Dr. Stephen Alexander Schuster, El Paso, and Miss Margery Castania White were married January 9.

Dr. Andrew B. Small, Dallas, and Miss Nancy Wright were married recently.

Dr. Isham Sellers Moore, Jr., Runge, and Miss Dorothy Cronin were married recently.

Deaths

Dr. Joseph Calvin Henderson, Waelder, aged 82, died recently.

Dr. Isaac N. Campbell, San Antonio, aged 67, died January 7 of endocarditis and blood stream streptococcus infection.

Dr. David W. Holmes, Bellevue, aged 73, died recently.

Dr. Josiah Green Smith, Port Arthur, aged 80, died January 3 of erysipelas.

Dr. Edmon Arthur Gilson, San Antonio, aged 64, died January 29 of bronchopneumonia.

Dr. Thomas W. Wilkinson, San Antonio, aged 67, died January 8 of coronary thrombosis and arteriosclerosis.

Dr. Phau Rivers Outlaw, El Paso, aged 67, died January 12 of pulmonary tuberculosis.

Dr. Bethune Freeman McDonald, Palestine, aged 44, died January 23 of coronary occlusion.

Dr. Thomas Rodger Knox, Uvalde, aged 75, died January 6.

Dr. Marshall Lee Austin, Montalba, aged 66, died recently.

Dr. Jess Autry Flautt, Galveston, aged 52, died January 19 of pneumonia.

Continued on page 44

THELESTRIN
OVARIAN FOLLICULAR HORMONE

A standardized preparation of the ovarian follicular hormone for intensive ovarian therapy by hypodermic injection.

Indicated in the treatment of scanty menstrual flow, amenorrhea and the vasomotor and nervous symptoms of the menopause.

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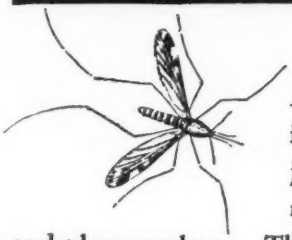

ATABRINE has received recognition not only in hundreds of published reports in medical journals throughout the world but also in a number of our standard textbooks on medicine and pharmacology. This constitutes a remarkable tribute to the important position which this relatively new drug occupies in the treatment of the various forms of malaria.

Atabrine has attained such prominence because of its manifold advantages over previous therapeutic agents. In the vast majority of cases, a short course with this drug produces quick extermination of the parasites, with prompt disappearance of the symptoms. Hence, as shown by numerous statistical studies, the possibility of relapses has been greatly reduced. Furthermore, Atabrine therapy has proved the most comfortable way of curing malaria.

Supplied in tablets of 0.1 Gm. (1½ grains), tubes of 15 and bottles of 100 and 500; 0.05 Gm. (¾ grain), bottles of 50 and 500. Ampules of 0.2 Gm., boxes of 5 (with distilled water).

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Continued from page 42

VIRGINIA

The Patrick Henry Medical Society has elected the following officers for the coming year: Dr. B. A. Hopkins, Stuart, President; Dr. E. M. McDaniel, Martinsville, Vice-President; Dr. Algernon K. Turner, Martinsville, Secretary-Treasurer.

Dr. Robert A. G. Jones has opened offices in Yorktown.

Dr. Charles H. Bondurant, formerly of Redford, has moved to Washington, D. C.

Dr. Charles William Reavis, Richmond, and Miss Allie Virginia Cleek were married recently.

Dr. Clifford H. Beach, Richmond, and Miss Jebbie Whitehead were married January 30.

Deaths

Dr. Albert Lincoln Winslow, Danville, aged 70, died January 13 of progressive muscular atrophy.

Dr. Emory William Reisinger, Fairfax, aged 65, died January 20 of mitral regurgitation and bronchopneumonia.

Dr. John Joseph Cullinan, Kecoughtan, aged 48, died February 26.

Dr. William Ashton Reese, Petersburg, aged 47, died March 21.

Dr. William Preston Hoy, Petersburg, aged 61, died March 23 following an operation.

Dr. Robert Lemmon, Lexington, aged 59, died March 6.

Dr. Baxter C. Culler, Martinsville, aged 39, died March 15 from lobar pneumonia.

WEST VIRGINIA

The West Virginia State Medical Association meeting will be held in Clarksburg May 24-26.

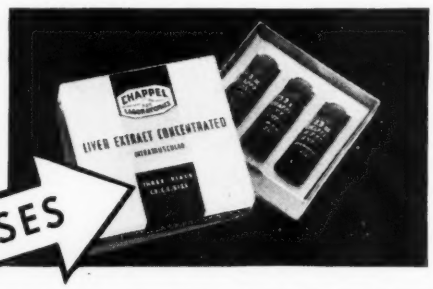
Deaths

Dr. John Thames, Charleston, aged 65, died January 11 of arteriosclerotic heart disease.

Dr. Benjamin Duncan Morrison, Wheeling, aged 72, died January 25 of diabetes mellitus.

Dr. O. L. Perry, Elkins, aged 75, died February 22.

Dr. W. W. Koiner, Beckley, aged 58, died February 22 of pneumonia.



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(Intramuscular)
for Effective, Simplified P.S. Management

Especially for the patient who balks at numerous injections is CHAPPEL LIVER EXTRACT CONCENTRATED (intramuscular) recommended. Reticulocytosis is achieved in most cases of pernicious anemia with one 3.3 cc. injection. Three to five such doses at intervals of from 7 to 10 days usually result in a complete hematological recovery; adequate maintenance can be established with one 3.3 cc. injection at 3 to 6 week intervals.

Improved methods of extraction and refinement minimize irritation. Each lot of Chappel Liver Extract is tested in one of the largest anemia clinics in the U. S. before release. . . Supplied in packages of three 3.3 cc. vials.

For Day-To-Day Injections — CHAPPEL LIVER EXTRACT (Subcutaneous) is sufficiently free from irritating substances to allow routine, safe and reactionless injections. The potent liver fractions are preserved, for effective and rapid regeneration in pernicious anemia. CHAPPEL LIVER EXTRACT is unusually economical.

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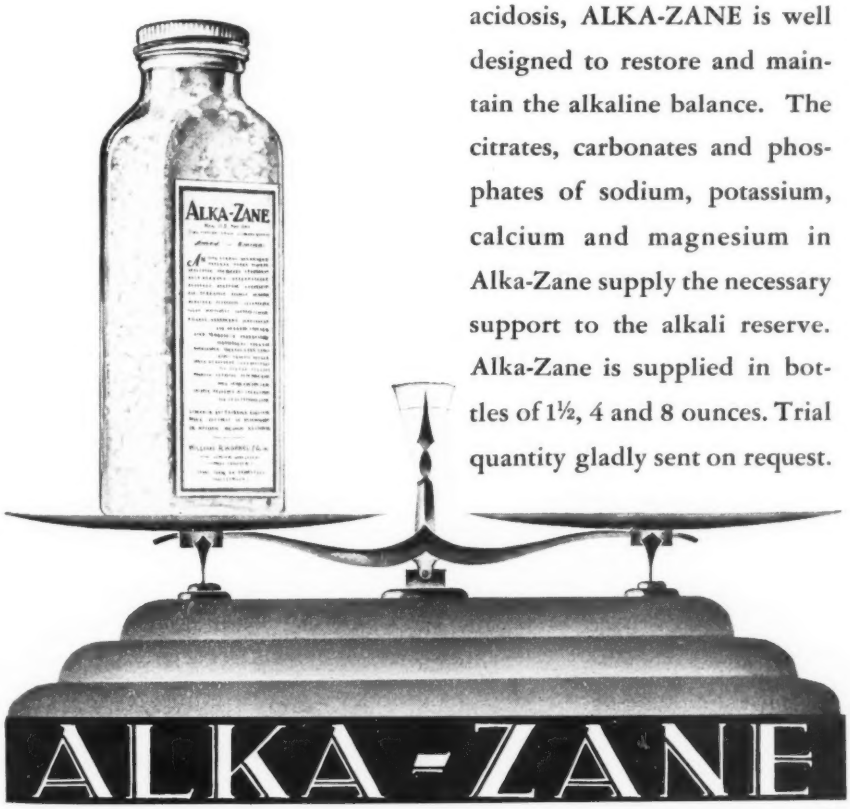
It may be a common cold or any febrile disease, it may be nephritis or liver disorder, general anesthesia or pregnancy . . . but whatever the cause of acidosis, ALKA-ZANE is well designed to restore and maintain the alkaline balance. The citrates, carbonates and phosphates of sodium, potassium, calcium and magnesium in Alka-Zane supply the necessary support to the alkali reserve. Alka-Zane is supplied in bottles of 1½, 4 and 8 ounces. Trial quantity gladly sent on request.



ALKA-ZANE

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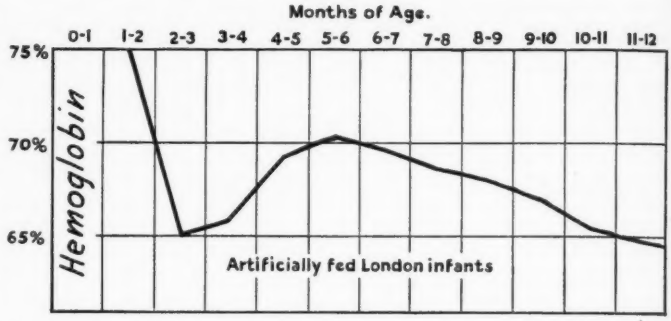
Nutritional Anemia in Infants

The accompanying chart of the hemoglobin level in the blood of infants is based on more than 1,000 clinical cases studied by Mackay. The sharp drop in hemoglobin during the early months of life has also been reported by a number of other authorities. It is noteworthy that this fall in hemoglobin has been found to parallel closely that of diminishing iron reserve in the infant's liver. The usual milk formula of infants in early life further contributes to this anemia because milk is notably low in iron. It is now possible, however, to increase significantly the iron intake of bottle-fed infants from birth by feeding Dextri-Maltose With Vitamin B in the milk formula. After the third month Pablum as the first solid food offers substantial amounts of iron for both breast- and bottle-fed babies.



Reasons for Early Pablum Feedings

1. The iron stored in the infant's liver at birth is rapidly depleted during the first months of life. (Mackay,[1] Elvehjem.[2])

2. During this period the infant's diet contains very little iron—1.44 mg. per day from the average bottle formulae of 20 ounces, or possibly 1.7 mg. per day from 28 ounces of breast milk. (Holt.[3])

For these reasons, and also because of the low hemoglobin values so frequent among pregnant and nursing mothers (Coons,[4] Galloway[5]), the pediatric trend is constantly toward the addition of iron-containing foods at an earlier age, as early as the third or fourth month. (Blatt,[6] Glazier,[7] Lynch[8].)

The Choice of the Iron-Containing Food

1. Many foods reputed to be high in iron actually add very few milligrams to the diet because much of the iron is lost in cooking or because the amount fed is necessarily small or because the food has a high percentage of water. Strained spinach, for instance, contains only 1 to 1.4 mg. of iron per 100 gm. (Bridges.[9])

2. To be effective, food iron should be in soluble form. Some foods fairly high in total iron are low in soluble iron. (Summerfeldt.[10])

3. **Pablum is high both in total iron (30 mg. per 100 gm.) and soluble iron (7.8 mg. per 100 gm.) and can be fed in significant amounts without digestive upsets as early as the third month, before the initial store of iron in the liver is depleted. Pablum also forms an iron-valuable addition to the diet of pregnant and nursing mothers.**

Pablum (Mead's Cereal thoroughly cooked and dried) consists of wheatmeal, oatmeal, cornmeal, wheat embryo, brewers' yeast, alfalfa leaf, beef bone, iron salt and sodium chloride.

[1-10] Bibliography on request.

MEAD JOHNSON & COMPANY, Evansville, Indiana, U. S. A.

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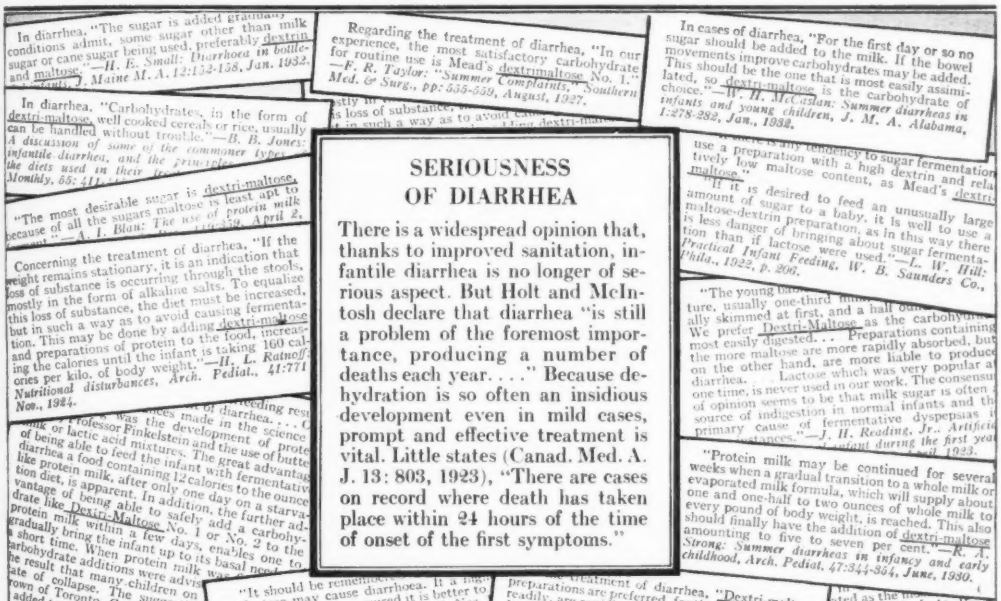
DIARRHEA

"the commonest ailment of infants in the summer months"

(HOLT AND McINTOSH: HOLT'S DISEASES OF INFANCY AND CHILDHOOD, 1933)

One of the outstanding features of DEXTRI-MALTOSE is that it is almost unanimously preferred as the carbohydrate in the management of infantile diarrhea.



SERIOUSNESS OF DIARRHEA

There is a widespread opinion that, thanks to improved sanitation, infantile diarrhea is no longer of serious aspect. But Holt and McIntosh declare that diarrhea "is still a problem of the foremost importance, producing a number of deaths each year. . . ." Because dehydration is so often an insidious development even in mild cases, prompt and effective treatment is vital. Little states (Canad. Med. A. J. 13: 803, 1923), "There are cases on record where death has taken place within 24 hours of the time of onset of the first symptoms."

Just as DEXTRI-MALTOSE is a carbohydrate modifier of choice, so is CASEC (calcium caseinate) an accepted protein modifier. Casec is of special value for (1) colic and loose green stools in breast-fed infants, (2) fermentative diarrhea in bottle-fed infants, (3) prematures, (4) marasmus, (5) celiac disease.

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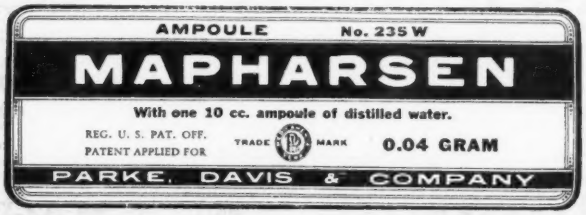

Mapharsen (meta-amino-para-hydroxy-phenylarsine oxide hydrochloride) is available in single-dose ampoules containing 0.04 and 0.06 gram, supplied in individual packages with or without distilled water. Also in ten-dose ampoules, for use by hospitals and clinics, containing 0.4 and 0.6 gram.

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